Assessment and Treatment of Malignant Pleural Effusions: Visual Analogue Scale, Ultrasound and Drainage

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Declaration of Originality

I, Eleanor Kate Mishra, hereby declare that this thesis contains the results of my own work except where otherwise acknowledged. The study on 'Determination of the minimal important difference of the visual analogue score for dyspnoea' (Chapter 2) was conceived of and designed and carried out by me with the assistance of Professor Robert Davies. 'Development of a thoracic ultrasound septation score' (Chapter 3) was conceived of and designed and carried out by me with the assistance of Dr Najib Rahman and Professor Fergus Gleeson. The TIME2 randomised controlled trial (Chapter 4) was designed by Dr Helen Davies and Professor Robert Davies who also obtained funding. I recruited patients, coordinated the trial, set up additional sites and co-authored the statistical analysis plan. Statistical analysis of TIME2 was performed by both myself and Brennan Kahan at the Medical Research Council. Information derived from the work of others and discussed in this thesis is referenced in the text and listed in the bibliography. No part of this thesis has previously been submitted in application for a higher degree.

Abstract

Assessment and Treatment of Malignant Pleural Effusions: Visual Analogue Scale, Ultrasound and Drainage

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This thesis consists of 3 studies:

1. **Determination of the minimal important difference (MID) of the visual analogue scale for dyspnoea (VASD)**: Determining the MID of the VASD is essential to interpret the results of trials in patients with malignant pleural effusions (MPEs). Patients undergoing a pleural procedure assessed the change in their VASD and the degree of change in their symptoms on a Likert scale. The mean VASD in patients experiencing a 'small but just worthwhile' decrease in their symptoms is the MID for the VASD and was found to be 22mm (95% CI 16 - 27mm).
2. **Development of a thoracic ultrasound septation score (TUSS)**: A TUSS is important for objectively assessing the degree of septation within a pleural effusion. An iterative process was used to demonstrate that degree of septation predicts clinical outcome, to identify candidate factors for inclusion in a TUSS and to determine which factors predicted the degree of septation. The final TUSS consisted of an assessment of the degree of homogeneity of septation distribution and number of septations at the most septated area.

3. **Effect of an indwelling pleural catheter (IPC) versus standard care for relieving dyspnoea in patients with MPEs: the TIME2 randomised controlled trial (RCT).** The objective of this unblinded RCT was to determine whether IPCs are more effective than chest drains and talc pleurodesis at relieving dyspnoea in patients with MPEs. 106 patients were randomised to either IPC or standard care in a 1:1 ratio. The primary outcome was daily VASD over 42 days post intervention. Dyspnoea improved in both groups with no significant difference in mean dyspnoea in the first 42 days (mean score: IPC 25mm (95% CI 19 – 30), standard care 24mm (95% CI 19 – 29).

Abstract word count: 280

Publications Arising from this Thesis

Paper

Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. Davies HE, Mishra EK (joint first authorship), Kahan BC, Wrightson JM, Stanton AE, Guhan A, Davies CW, Grayez J, Harrison R, Prasad A, Crosthwaite N, Lee YC, Davies RJO, Miller RF, Rahman NM. JAMA 2012 Jun 13;307(22):2383-9.

Abstracts

Mishra EK, Davies HE (joint first authorship), Wrightson JM, Stanton A, Guhan A, Davies C, Grayez J, Harrison R, Prasad A, Crosthwaite N, Lee YCG, Miller RM, Kahan BC, Rahman NM. The second therapeutic intervention in malignant effusion trial (TIME2): a randomised controlled trial to assess the efficacy and safety of patient controlled malignant pleural effusion drainage by indwelling pleural catheter compared to chest drain and talc slurry pleurodesis. European Respiratory Society conference (2012).

Davies HE, Mishra EK (joint first authorship), Wrightson JM, Stanton A, Guhan A, Davies C, Grayez J, Harrison R, Prasad A, Crosthwaite N, Lee YCG, Miller RM, Kahan BC, Rahman NM. The Second Therapeutic Intervention in Malignant Effusion Trial (TIME2): A Randomised Controlled Trial to Assess the Efficacy and Safety of Patient Controlled Malignant Pleural Effusion Drainage by Indwelling Pleural Catheter

Compared to Chest Tube and Talc Slurry Pleurodesis. American Thoracic Society conference (2012).

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This thesis is dedicated to the memory of Professor Robert Davies.

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Abbreviations used in this Thesis

ARDS	Acute respiratory distress syndrome
AE	Adverse event
ANOVA	Analysis of variance
CI	Confidence intervals
CR10	Category ratio 10
CRF	Case report form
CT	Computerised tomography
CXR	Chest radiograph
CRDQ	Chronic Respiratory Disease Questionnaire
EORTC QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	European Quality of Life (EuroQol) 5 Dimensions Questionnaire
ERES	Empirical rule effect size
ES	Effect size
FDG PET	18-fluorodeoxyglucose positron emission tomography imaging
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity

GP	General practitioner
IL	Interleukin
IPC	Indwelling pleural catheter
IQR	Interquartile range
LAT	Local anaesthetic thoracoscopy
MCP	Monocyte chemoattractant protein
MID	Minimal important difference
MMP	Matrix metalloproteinase
MPE	Malignant pleural effusion
MRC CTU	Medical Research Council Clinical Trials Unit
NSCLC	Non-small cell lung cancer
ORTU	Oxford Respiratory Trials Unit
PI	Principal Investigator
PS	Performance status
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SEM	Standard error of measurement
SP	Spontaneous pleurodesis

TGF	Transforming growth factor
TIME2	Second Therapeutic Intervention in Malignant Effusion Trial
TIME3-UK	Third Therapeutic Intervention in Malignant Effusion Trial
TIMP	Tissue inhibitor of metalloproteinase
TUSS	Thoracic ultrasound septation score
UK CRN	United Kingdom Clinical Research Network
US	Ultrasound
VAS	Visual analogue scale
VASD	Visual analogue scale for dyspnoea
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation

1 Introduction

Malignant pleural effusions (MPEs), defined as the accumulation of fluid in the pleural space secondary to cancer, cause disabling breathlessness and impair quality of life in over 1 million people worldwide per year [1, 2]. Improving treatment of these patients is a priority for respiratory research. This DPhil thesis reports my research on two tools for investigating the clinical impact of MPEs and one clinical trial comparing different treatments for the palliation of symptoms associated with MPEs. In this introduction, I review the causes, incidence and pathology underlying the development of MPEs and review evidence for current management.

1.1 Causes of malignant pleural effusions

MPEs can be caused by primary pleural malignancy, usually malignant mesothelioma, or by metastatic cancer from other sites. Lung cancer is the commonest metastatic cause of a MPE, responsible for one third of all cases, followed by breast cancer (25%), lymphoma (10%), ovarian cancer (5%), gastric cancer (2%) and unknown primaries (7%)[3].

1.2 Incidence

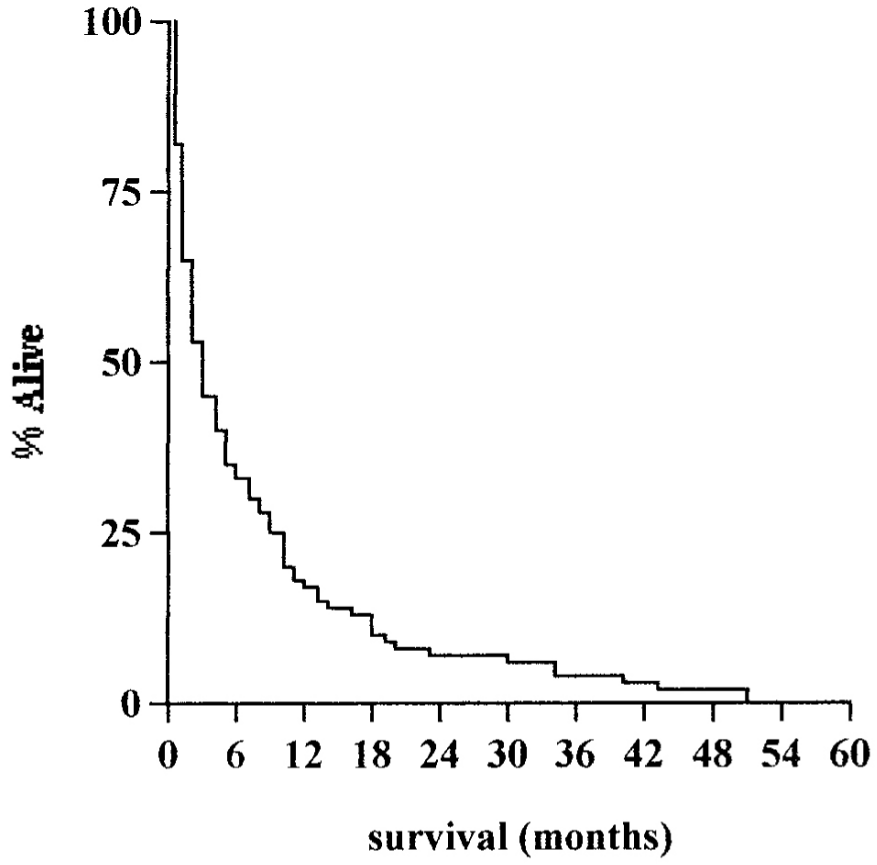
Pleural effusions affect 0.3% of the population per year, and up to 70% of all exudative effusions are secondary to malignancy [4, 5]. This extrapolates to an incidence of 260,000/MPEs year in the UK and USA combined. At post mortem, 15% of patients who die of cancer have a malignant pleural effusion[2]. Malignant pleural effusions are

increasing in prevalence as the incidence of carcinoma rises in an aging population and therefore the incidence is predicted to treble by 2030[6, 7]. Lung cancer is the commonest cancer worldwide, with an estimated 1.61 million new cases each year, of which 30.5% will develop an effusion[8, 9]. For breast cancer, the European age-standardised incidence rate for women in Britain increased by 65% in the thirty years from 1979 to 2008 and approximately 5% of these patients develop a pleural effusion as the first sign of distant clinical metastases[10, 11]. Mesothelioma causes symptomatic pleural effusion in about 95% of cases and in the UK is predicted to increase in incidence until 2020 with an estimated 65,000 patients dying of this disease between 2001 and 2050[12-14].

1.3 Prognosis

Malignant pleural effusion is a poor prognostic marker, often indicating advanced disease. Median survival is only 3-4 months [15]. Patients with a good performance status (PS) (Karnofsky score ≥70) have a median survival ten times greater than patients with poor PS (Karnofsky score ≤30)[16]. However, there is a wide variation in prognosis, with a small proportion of patients surviving for a few years(Figure 1-1).

Figure 1-1 Kaplan-Meier curve demonstrating survival in a group of patients with MPEs. Reproduced from Burrows et al.[16]



1.4 Aetiology of malignant pleural effusions

In health, pleural fluid is filtered from the parietal systemic circulation into the pleural space, and exits via lymphatic stomata between mesothelial cells in the parietal pleura. The fluid drains via the intercostal lymphatics to the mediastinal lymph nodes[17]. The normal pleural fluid volume is approximately 8ml in each pleural space[18]. MPEs accumulate as a result of both increased production and decreased absorption of pleural fluid.

Neovascularization is common in malignant pleural disease and is, in part, induced by angiogenic factors from tumour cells, particularly

vascular endothelial growth factor (VEGF). The new blood vessels are hyperpermeable which results in leakage of fluid, protein and blood cells, and generation of an exudative, often blood-stained, effusion[19, 20]. Yano et al. showed that human adenocarcinoma lung cancer cells frequently caused MPEs in a mouse model, whereas squamous cell cancer cells did not[19]. They hypothesised that this is due to the more peripheral location of adenocarcinoma metastases allowing invasion of the pleura, and to the higher levels of VEGF produced by adenocarcinoma cells. In humans, a positive correlation is seen between pleural fluid volume and VEGF levels. Baseline VEFG levels are associated with reduced survival in patients with non-small cell lung cancer (NSCLC)[21].

Malignant infiltration into lymphatics slows drainage of pleural fluid. Post mortem series have shown that the development of an effusion relates to malignant infiltration of mediastinal lymph nodes, not to the extent of pleural involvement by metastases[22, 23]. Therapies which attempt to treat MPEs by targeting production of pleural fluid alone will not be effective in patients in whom lymphatic infiltration is the primary cause of the effusion.

1.5 Pathobiology of pleural metastases

Knowledge of the molecular biology underlying the development of pleural metastases and MPE remains limited, which in part contributes to the relative lack of translational advances and novel therapies.

1.5.1 Spread of malignant cells to the pleura

Malignant cells often spread as tumour emboli from cancer foci in the lung, to the parenchymal tissue and subsequently into the pleura. Direct invasion and haematogenous or lymphatic spread can also occur[2, 23, 24]. Following visceral pleural involvement, cells then spread to the parietal pleura either across adhesions or freely through the pleural fluid[2, 23]. Peripheral tumours are more commonly associated with pleural invasion and pleural effusions[19].

1.5.2 Anchoring and proliferation of cancer cells in the pleura

For tumour cells to anchor onto pleural tissues and continue to expand, they need to adhere to the mesothelial surface, be able to proliferate and to avoid immune surveillance. Numerous mediators have been postulated to play a role in vitro, although few have been tested in animal models, let alone humans.

Cytokines such as transforming growth factor-beta (TGFβ), matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinase (TIMP) are important in the regulation of matrix formation (which aids cancer cell anchoring to pleural tissue). Batimastat, a MMP inhibitor, led to a decrease in the frequency of pleural aspiration in a phase 1 trial for treatment of MPE[25].

1.5.3 Angiogenesis

Exudative pleural effusions are thought to accumulate due to increased levels of VEGF. VEGF levels are higher in malignant pleural

effusions than in other effusions and relative to matched serum concentrations[26-29]. VEGF stimulates angiogenesis, but the new blood vessels which develop are hyperpermeable, resulting in leakage of fluid, protein and blood cells, and generation of an exudative, often blood-stained, effusion[19, 20]. In humans, a positive correlation is seen between pleural fluid volume, VEGF levels, pleural fluid pH and glucose[28, 30]. Other angiogenic mechanisms, including osteopontin and the angiopoietin/Tie2 axis have also been implicated in the development of MPEs[31, 32]. Recent research in mice has suggested a role for monocyte chemoattractant protein (MCP)-1 in the development of MPEs, with tumour cells expressing high levels of MCP-1 associated with increased volume of pleural fluid, greater vascular permeability and angiogenesis, compared to tumour cells expressing low levels[33]. Bevacizumab, a monoclonal antibody VEGF antagonist, has been approved for the initial treatment of patients with unresectable, locally advanced, recurrent or metastatic, nonsquamous non-small cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel chemotherapy following an RCT demonstrating an improvement in overall survival compared to chemotherapy alone (median overall survival 12.3 versus 10.3 months)[34]. It has also been used with beneficial effect in small numbers of patients with recurrent benign pleural effusions[35, 36].

Recent preclinical work has presented several other potential therapeutic targets. For example, inhibition of NK-κB in mouse models decreases TNF-α levels in MPE, tumour burden and pleural fluid volume[37]. Also, bisphosphonates prevent adhesion to the extracellular

membrane, perhaps by decreasing the levels of adhesion molecules and reducing MMP-9 release into the pleural space, and may have a role in the treatment of MPE. In particular, zoledronic acid, a nitro-bisphosphonate, has shown particular promise in a mouse model of lung cancer induced MPE: daily subcutaneous administration of zoledronic acid reduced tumour load, vascular hyperpermeability, in vivo fluid accumulation and improved survival[38]. Other anti-angiogenic approaches e.g. use of endostatin, are being explored[39].

1.5.4 Intrapleural immune defences against spread of malignant cells

The intrapleural immune system defends against invasion of malignant cells, which, in turn, develop mechanisms to overcome this and continue replicating. Mesothelial cells and intrapleural dendritic cells are part of the innate immune response and act as antigen-presenting cells that prevent tumour cell invasion of the pleura. They attract lymphocytes and macrophages to the pleural space via intercellular adhesion molecule-1 and toll-like receptor-2, causing a lymphocytic effusion[40, 41]. Manipulation of the intrapleural immune system offers another experimental therapeutic target for the management of MPE. Potential immunotherapies for MPE include macrophage stimulation by MDP-Lys, a synthetic muramyl dipeptide derivative, and OK-432, a streptococcal preparation that induces a local immune response[42, 43]. New therapies focusing on dendritic cell based immunotherapy are under phase I clinical assessment in mesothelioma and may be useful for other MPEs.

In response to host defences, malignant cells induce a locally immunosuppressive state in MPE, triggering high levels of interleukin (IL)-4, IL-10, TGF-α and TGF-β and low levels of IL-2, IL-12, IL-18 and interferon-gamma and a Th2 type immune response[44, 45]. The CD4+CD25- T lymphocytes found in MPEs have low tumour cytolytic activity[46]. Tumour-associated macrophages may also be exploited by malignant cells to aid tumour progression via release of growth factors and cytokines[47].

1.6 Clinical features

Common symptoms in patients presenting with MPE are breathlessness, cough and chest pain but some patients are asymptomatic[48]. Clinical history is unreliable in predicting whether an effusion is malignant or benign. However, symptoms associated with a higher likelihood of an underlying malignancy are: dull (rather than pleuritic) chest pain; work exposure to carcinogens; a shorter history of disease symptoms; severe breathlessness; absence of fevers; and a personal history of cancer[49]. As well as signs of a pleural effusion, patients with cancer may have other evidence of advanced malignancy, such as cachexia and lymphadenopathy[22].

MPE causes dyspnoea via a variety of pathophysiological changes. The extra volume of the pleural fluid is compensated for mainly by an increase in the longitudinal size of the thoracic cavity, causing less compression of lung than would be expected from the volume of fluid. For every litre of pleural fluid drained, the forced vital capacity only increases on average by about 200mL, and the total lung capacity by

about 500mL[50]. The weight of the pleural fluid can lead to inversion of the hemidiaphragm, leading to compression of the hemithorax when the diaphragm contracts during inspiration rather than normal expansion. Dyspnoea is often more significant in patients whose diaphragm is inverted[51].

Most patients with moderate or large pleural effusions have abnormal arterial blood gases, primarily a low PaO_2. The main mechanism underlying this hypoxemia is an intrapulmonary shunt which does not change significantly immediately after thoracentesis; hence blood gas results often do not improve, and reexpansion pulmonary oedema within the lung may even lead to deterioration after fluid evacuation[50].

Breathlessness in patients with lung cancer and malignant effusions often involves extrapleural factors in addition to the factors discussed above. Concurrent infection, atelectasis, pulmonary embolism, lymphangitis and pericardial involvement must be considered. The relative contribution of pleural disease can only be assessed upon removal of the pleural fluid.

1.7 Investigations

1.7.1 Imaging

Imaging is essential to confirm the presence of a pleural effusion.

1.7.1.1 Chest radiography

A pleural effusion is usually first confirmed on a CXR which can be abnormal with as little as 200ml of fluid. Pleural deposits and thickening

may also be seen. Up to 15% of patients with lung cancer have a pleural effusion demonstrable on CXR at diagnosis[52-54]. CXR also can suggest diagnosis of a trapped lung following pleural fluid drainage and is useful to assess for fluid re-accumulation on follow up.

1.7.1.2 Thoracic ultrasonography

Thoracic ultrasonography (US) is becoming increasingly important in the investigation and management of pleural effusions. Not only is it more sensitive for the detection of pleural fluid than CXR, it can also distinguish between pleural fluid and thickening, and guide pleural drainage and pleural biopsy, particularly if the effusion is small or loculated[1]. US-guided thoracentesis has been shown to be safer than blind pleural aspiration, even in experienced hands[55, 56].

Ultrasound can distinguish MPEs from other causes of effusions, with a sensitivity of 73% and specificity of 100% for malignancy[57]. Pleural metastases may be seen as dark regions of pleural thickening with irregular or indistinct borders, or pleurally based masses that may be seen invading neighbouring structures[58]. Other features of malignant effusions are pleural thickening measuring greater than 7mm and an echogenic swirling pattern visible in the pleural fluid[59]. Physician-performed ultrasonography is rapidly gaining acceptance and imaging guidance is recommended by many regulatory bodies for chest drain insertion and other pleural procedures[60]. US studies of pleural effusions have categorised pleural effusions into anechoic, complex septated, complex nonseptated and homogenous echogenic effusions but no attempt has been made to subcategorise septated pleural

effusions[61]. US is not useful for detecting deeper pockets of pleural fluid, such as fluid that has become encysted in the horizontal fissure, as US waves do not penetrate through the air of the lung.

1.7.1.3 Computerised tomography

Computerised Tomography (CT) is another important modality in investigating patients with pleural effusion. Up to 25% of patients with lung cancer have a pleural effusion on CT at the time of presentation[8]. In patients with an undiagnosed pleural effusion, CT should be performed with pleural-phase contrast enhancement to aid detection of pleural abnormalities. Malignant pleural disease is suggested by the presence of pleural thickening which is >1 cm thick, nodular, circumferential or extending onto the mediastinal surface[62]. Pleural septations are not visible on CT, but loculations are visible, which suggest septated, difficult to drain fluid. CT is useful for detecting deeper pockets of pleural fluid.

1.7.1.4 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is useful for identifying areas of chest wall involvement by lung cancer[63]. It has the advantage over CT that it does not involve ionising radiation but is rarely used in clinical practice to assess patients with MPEs due to longer scan durations, decreased patient tolerability and longer waiting times compared to CT. Septations in pleural fluid are clearly visible on MRI, but no study has been performed comparing US and MRI for assessment of septations.

1.7.1.5 18-fluorodeoxyglucose positron emission tomography imaging

Although not part of routine investigations of a malignant pleural effusion, 18-fluorodeoxyglucose positron emission tomography imaging (FDG PET) is a sensitive and specific method of distinguishing between benign and malignant disease in exudative pleural effusions and pleural thickening: It identifies malignancy with a sensitivity of 96.8-100% and specificity of 88.5-94.8% in selected populations and may also be useful in detecting dry pleural dissemination[64-66]. Other inflammatory causes of pleural effusions such as parapneumonic or tuberculous effusions can also lead to avid FDG uptake, as can previous talc pleurodesis, therefore correlation with CT findings are required[67]. Uptake is greater in thoracic than extrathoracic primary malignancies[68]. High standard pleural uptake values are predictive of a poorer prognosis in patients with non-small cell lung cancer[69]. PET also has the advantage of identifying other sites of disease spread. Avid FDG uptake can persist in the pleural space following talc pleurodesis for at least 20 years, which may be a disadvantage if PET becomes used more commonly by oncologists to assess disease response and may lead to the development of novel pleurodesis agents which do not cause the same problem[70].

1.7.2 Pleural fluid analysis

Demonstration of malignant cells in the pleural cavity, by cytology or biopsy, defines a malignant effusion and may provide information on

the underlying malignancy to guide treatment. No biochemical or tumour markers can reliably determine a malignant effusion.

1.7.2.1 Pleural fluid appearance

The appearance of the pleural fluid is not diagnostic. Although haemorrhagic effusions often raise concern about malignancy, only 50% of haemorrhagic effusions turn out to be malignant; conversely, only 10% of MPEs are haemorrhagic.

1.7.2.2 Exudates and transudates

Malignant effusions are usually exudates, though approximately 5% are transudates - usually a result of a concurrent transudative cause (e.g. heart failure)[3].

1.7.2.3 Pleural fluid pH

A low pleural fluid pH (<7.3) reflects more extensive tumour load in the pleura, a higher chance of positive pleural fluid cytology, a lower success rate of subsequent pleurodesis, and a poorer prognosis[71, 72]. The pleural fluid glucose level generally parallels the pleural fluid pH.

1.7.2.4 Pleural fluid cytology

Pleural fluid should be sent for cytological examination, which has a sensitivity of about 60% for malignancy[73]. The sensitivity is dependent on tumour type, extent and experience of the cytologist. A volume of 20ml is sufficient and volumes greater than 50ml do not improve sensitivity[74, 75]. Although repeat thoracentesis can increase the sensitivity of cytological diagnosis, the additional yield decreases sharply with each subsequent sample e.g. one series of fluid samples,

including pleural fluid, found an initial yield of 65%, with an additional yield of 27% with a second sample and only 5% with a third sample[76]. Pleural biopsy should be considered if the initial cytologic analysis fails to provide a diagnosis.

1.7.2.5 Biomarkers for malignant pleural effusions

Malignant pleural effusions account for approximately 40% of all exudative effusions but pleural fluid cytology is positive in only 60% of cases, leading to a need for further diagnostic tests. Identification of pleural fluid biomarkers that are able to discriminate malignant pleural effusion from other causes of exudative effusions would help rapid diagnosis. Many biomarkers have been shown to be increased in concentration in malignant pleural effusions compared to benign disease, including VEGF, endostatin, MMPs and tumour markers such as carcinoembryonic antigen[39, 77-79]. Of these markers, pleural fluid mesothelin appears to show the most promise for clinical use, with a sensitivity of 71% and a specificity of 89% for the diagnosis of malignant mesothelioma[80]. Mesothelin is unusual in being relatively specific for the diagnosis of mesothelioma, whereas most other biomarkers are unable to distinguish between different primary cell types[81]. However, mesothelin is unable to differentiate between epithelioid and sarcomatoid mesothelioma, which have significantly different prognoses, and adenocarcinoma may lead to a false positive result.

Other tumour markers such as CA 125 and CA 15-3 have a limited benefit in the diagnosis of malignant pleural effusions, although their

sensitivity and specificity can be increased by using two or more in combination[82].

Other limitations of these biomarkers compared to cytology and biopsy are that they lack the specificity required to make a definite diagnosis of cancer and they do not provide information about specific receptor expression, knowledge that is increasingly important to guide treatment.

Pleural fluid biomarkers for malignancy have been used to attempt to predict prognosis in patients with malignant pleural effusions, important in order to determine the optimal treatment for these patients. Although high levels of tumour markers and low pH are predictive of a poor prognosis, these measurements are not sufficiently correlative to be able to determine correct treatment for an individual patient[83].

1.7.3 Pleural biopsy

If the cause of a pleural effusion remains undiagnosed following initial aspiration, pleural biopsy is key to diagnosis. Image guided biopsy, with CT or US, and thoracoscopy have largely replaced blind biopsy due to their greater sensitivity and safety profile. Pleural biopsy allows more precise histological diagnosis in the case of cytology proven malignancy and can identify the genetic profile of the malignant cells, enabling individually tailored treatment.

Image guided biopsy using CT has been shown to have a sensitivity of 87% compared to Abrams' needle biopsy, which has a sensitivity of 47%[84]. It is the initial biopsy method of choice in pleural thickening

and may be useful when medical thoracoscopy has failed. US guided biopsy is increasingly being used as an alternative and demonstrates a sensitivity of 80%[85]. It has the advantage that it can be performed by respiratory physicians with access to and training in thoracic ultrasound, whereas CT is limited to radiologists.

Thoracoscopy (also known as pleuroscopy) can either be performed under general anaesthetic, commonly termed video assisted thoracoscopy (VATS), or using sedation and local anaesthetic, often called medical or local anaesthetic thoracoscopy (LAT). Medical thoracoscopy can either be performed using a rigid or semirigid thoracoscope. Medical thoracoscopy has the advantage over other biopsy techniques that it allows therapeutic removal of pleural fluid and pleurodesis during the same procedure as diagnosis. Medical thoracoscopy has a diagnostic yield of 85-100% for malignancy[86, 87]. Additionally, assessment of the extent of pleural adhesions during thoracoscopy provides prognostic information in patients with malignant pleural effusions, with patients with minimal or no adhesions having a medial survival of 9 months compared to 5 months in those with high levels of adhesions[88]. Complications include empyema and pleural bleeding, but mortality is extremely low. Redo medical thoracoscopy is possible in patients with pleural disease if indicated, without an increase in morbidity or mortality although a greater number of adhesions may be encountered[89].

1.8 Treatment of Malignant effusion

The aim of treatment of patients with MPEs is to palliate symptoms

with minimal side effects, disruption to life, hospital stay and cost, thereby improving overall quality of life. For patients with an asymptomatic malignant effusion, no intervention is required and they can remain under observation. Strategies for management of recurrent malignant effusion can be divided into four categories:

1. Removal of pleural fluid;
2. Obliteration of the pleural space to avoid fluid re-accumulation (i.e. pleurodesis);
3. Systemic therapy aimed at treating the underlying cause; and
4. Palliation of dyspnoea.

There is interest in the use of intrapleural anticancer agents in patients with MPEs to help localise these agents to areas of cancer, thereby reduced the rate of side effects, but this remains experimental at present[90, 91].

In a minority of patients, particularly those with highly chemotherapy responsive tumours such as small cell lung cancer and lymphoma, systemic chemotherapy alone may be effective treatment. However, the majority of patients will require pleural aspiration to relieve breathlessness and, in 70–90% of these, symptomatic re-accumulation following drainage occurs, and pleurodesis is required. No clinical or biochemical factors reliably predict which effusions will recur and the choice of subsequent treatment must take into account the rate of fluid accumulation, associated symptoms, and the patient's prognosis.

In cancer patients, with multiple potential causes of breathlessness, therapeutic thoracentesis may be the most direct way to

establish the relative contribution of the pleural effusion to the dyspnoea. Evacuation of pleural fluid relieves breathlessness by restoring the mechanical advantage of the diaphragmatic muscles. It does not prevent fluid recurrence and only provides short term symptom relief. Re-expansion pulmonary oedema is a rare but potentially fatal complication when ipsilateral pulmonary oedema occurs following rapid removal of a large volume of pleural fluid, especially if the underlying lung has been collapsed for a period of time. The 2001 Joint European Respiratory Society and American Thoracic Society statement entitled 'Management of Malignant Pleural Effusions' recommends monitoring pleural fluid pressure by manometry during the procedure and to stop if the pleural pressure falls below -20cmH_2O[92]. However manometry is not widely available; pragmatically, clinicians are advised not to remove more than 1.5L of fluid on each occasion and to discontinue aspiration if the patient develops dyspnoea, chest pain or cough (signs of rapid pulmonary expansion). In patients with advanced disease, a limited life expectancy (i.e. < 2 months) or poor performance status, repeated thoracentesis has traditionally been thought to be an appropriate way to manage pleural fluid reaccumulation, rather than pleurodesis.

1.8.1 Chest drain and pleurodesis

Standard care in symptomatic patients with recurrent MPE is to admit the patient to hospital for chest drain insertion and pleurodesis. This should only be considered in patients who have symptom relief following thoracentesis. Pleurodesis is the artificial symphysis of the visceral and parietal pleural surfaces, done to prevent symptomatic pleural fluid recurrence. It is usually performed by injecting an irritant

into the pleural space, but it can be performed by mechanical abrasion during thoracic surgery.

1.8.1.1 Talc pleurodesis

Many different agents have been used as an irritant for to induce pleurodesis, but randomised trials of different agents appear to confirm that talc is as effective or more effective agent than other drugs, with a 30-day success rate of approximately 75%[93-96]. However, reports of acute respiratory distress syndrome (ARDS) following talc pleurodesis have led to a reappraisal of its use. A prospective study of talc pleurodesis demonstrated a 3% treatment-related mortality and 10% of patients suffered respiratory complications[93]. Randomised trials comparing ordinary mixed talc, where the mean particle size was less than 15microns, versus graded talc, in which most particles <10microns had been removed, demonstrated a significant increase in lung inflammation and a deterioration in gas exchange in patients receiving the mixed talc[97]. The small particles appear to be able to enter the systemic circulation and cause bilateral lung inflammation, leading in extreme cases, to ARDS and death[98]. A prospective cohort study of 558 patients undergoing pleurodesis, demonstrated that graded talc appears to be safe with no cases of ARDS[99]. In response to this research, the UK Medicines and Healthcare Products Regulatory Authority reclassified talc as a medicinal product and removed its licensed use as a medical device[100].

Talc can be administered as a poudrage during thoracoscopy or a slurry injected via a chest drain. Recent randomised trials comparing the

two showed they were equivalent, although a post hoc subgroup analysis in one trial suggested that patients with breast and lung cancer may have a better result with talc poudrage[93, 101]. Conventionally it is believed that as poudrage allows a more uniform delivery of talc over the pleural surface, which carries a theoretical advantage of efficacy, but there is little scientific evidence to support this argument. Radio-active labelled talc studies have shown that talc distributes effectively around the pleural cavity as a slurry and that rotating the patient is unnecessary[102]. Talc acts by inducing an acute inflammatory response which, if sufficiently intense, results in eventual pleural fibrosis and adhesion formation.

Contraindications to pleurodesis include a poor prognosis (generally, but arbitrarily, accepted as <3 months) and failure of apposition of the pleural surfaces (trapped lung). Trapped lung occurs when lung expansion is restricted, either by visceral pleura tumour encasement or by endobronchial obstruction. Creation of pleural fibrosis to bridge the two pleural surfaces is not feasible with underlying trapped lung and attempts at pleurodesis may induce additional visceral thickening, further restricting lung expansion. Bilateral talc pleurodesis should not be performed at the same time, due to the potential hypoxia associated with talc administration.

There is a wide variation between physicians in the timing of pleurodesis for MPE. Some advocate pleurodesis at diagnosis whereas others delay until symptomatic recurrence has occurred[103]. Early pleurodesis, before the possible development of trapped lung, may

theoretically allow a higher success rate, though this has not been formally tested.

1.8.1.2 Other pleurodesis agents

Other available pleurodesis agents are less effective than talc, but may be preferable in patients with significant hypoxia or concomitant respiratory disease[95, 104, 105]. These include: cyclines, e.g. tetracycline (1500mg or 20 mg/kg) and doxycycline (500mg); and bleomycin (15-240 units). OK-432, a preparation of *Streptococcus pyogenes* type A3, is often used for pleurodesis in Japan, and quinacrine is popular in Scandinavia[106][107].

New agents are being developed, stimulated by limitations of current pleurodesis agents and a greater understanding of the molecular mechanisms of pleurodesis. TGF-β, a potent mediator of fibrosis, shows promise in animal models, and a recent phase I study utilising intrapleural lipoteichoic acid-T, an novel agent based on a bacterial cell wall motif, confirmed safety for intra-pleural administration in humans[108]. This area will be the focus of much future research.

1.8.2 Indwelling pleural catheters

Long-term indwelling pleural catheters (IPCs) are an alternative to chest drain and pleurodesis, and this DPhil thesis reports a clinical trial comparing IPCs with chest drain and pleurodesis. IPCs will be discussed further in Chapter 4.

1.8.3 Intrapleural fibrinolytics

In symptomatic patients with a septated or loculated malignant pleural effusion, which is not draining despite the presence of an patent chest drain, intrapleural fibrinolytics offer improved drainage, but it is not known whether this translates into clinically significantly outcomes, such as relief of breathlessness and pleurodesis success[109, 110].

1.8.4 Palliation of dyspnoea

For some patients a non-invasive approach to their pleural effusion is appropriate e.g. those with a grave prognosis or who refuse pleural intervention. Use of opiates, oxygen, sedatives and anxiolytic agents should be used to afford symptom relief.

1.9 The aims of this Thesis

This thesis aims to improve treatment for patients with malignant pleural effusions through both developing tools for clinical research and reporting a clinical trial (TIME2) into the treatment of MPEs. Firstly, I will discuss research to determine the minimal important difference (MID) in the visual analogue scale for dyspnoea (VASD), the measure of dyspnoea which is used in TIME2. Secondly, research will be presented to develop and validate a septation score for categorising the degree of septation within pleural effusions. This score will be a tool for clinicians to use to assess which MPEs require fibrinolytics and to guide other treatment choices. TIME2 (The Second Therapeutic Intervention in Malignant Effusions Trial) is a RCT comparing IPCs with chest drain and pleurodesis, specifically assessing which is more effective at relieving breathlessness. My research also involved setting up and running a

second clinical trial, TIME3-UK (Adjuvant Urokinase in the Treatment of Malignant Pleural Effusion: the Third Therapeutic Intervention in Malignant Effusion Trial). This is an RCT comparing intrapleural urokinase, a fibrinolytic, with placebo to assess whether the improved drainage observed translates into clinically significant outcomes, specifically relief of dyspnoea and pleurodesis success. However, this trial is continuing to recruit and will not be reported in this thesis.

1.10 Summary

MPEs are a common clinical problem and cause disabling breathlessness. This DPhil thesis reports work done to provide an evidence base for clinicians to select appropriate methods for treating their patients.

2 Determination of the minimal important difference of the visual analogue score for dyspnoea in patients with malignant pleural effusions

2.1 Introduction

The minimal important difference (MID) is the smallest worthwhile change in symptoms as measured by a particular tool, which can be a questionnaire or objective clinical measurement. It is essential for interpreting the results of a clinical trial. The primary outcome measure for the 2 clinical trials included in the work of my research, of which TIME2 is reported in this thesis, is mean daily dyspnoea as determined by the visual analogue scale for dyspnoea (VASD). In order to assess the clinical significance of the results of these trials, the MID for the VASD must be determined. Determining the MID for the VASD is also important for determining the sample size required for further studies of MPEs. Despite it's importance, the MID of the VASD has not previously been determined in patients with MPEs and only small studies have assessed it in other patient groups. The aim of this study is to use a combination of techniques to determine the MID for the VASD in patients with MPEs.

The VASD is a 100mm horizontal line anchored at 0mm with 'Not breathless at all' and at 100mm with 'Worst possible breathlessness'. Patients are asked to draw a vertical line crossing the VASD at a point

which represents their level of breathlessness. The score is calculated by measuring in millimetres from 0mm to the patient's line. Dyspnoea is a subjective symptom and the VASD is a means of converting this into a numerical value.

2.1.1 Definition of MID

There is no universally agreed definition of the MID, with different researchers choosing to use different definitions. I have chosen to use the following definition: 'the smallest difference in score in the outcome of interest that patients perceive as worthwhile, and that would lead the patient or clinician to consider a change in the management'[111].

I have chosen this definition because it is determined primarily by the patient, and it encompasses a trade off between the benefits and disadvantages of a treatment. Given that dyspnoea is a subjective experience, I consider that it should be the subject experiencing the symptom who determines whether a change in symptoms is worthwhile. Previous researchers have used the opinions of experienced healthcare professionals to determine the MID, but I do not consider this approach to be valid for a subjective sensation such as dyspnoea. This definition suggests that the MID will be specific to a specific management option i.e. the MID for the VASD may be different for therapeutic aspiration than for chest drain and pleurodesis. This is appropriate, as the symptomatic benefit a patient considers worthwhile will be different for different interventions depending on convenience, side effects and length of hospital stay.

Other researchers have equated the MID to the 'just noticeable difference', stating 'a difference in functional status scores is clinically important if it is associated with a difference that a typical patient can notice'[112]. It may be true that, for some conditions and treatments with minimal side effects and inconvenience to the patient, the MID will be equivalent to the just noticeable difference. However, for patients with MPEs undergoing invasive procedures which carry a significant risk and may required a prolonged hospital stay, the MID will be greater than the 'just noticeable difference'.

2.1.2 Importance of the MID

Determining the MID is important for researchers when planning and interpreting the results of clinical trials and for clinicians and patients when deciding what treatment is appropriate. When determining the required sample size for a clinical trial, the MID is essential for a power calculation, in which it is used as the value for delta, and will mean the trial will produce clinically meaningful results. Equally, knowing the MID allows researchers to determine whether the results of their work should change clinical practice. Trials should be adequately powered based on the MID. If not, this may lead to false positive results, which are statistically significant but not clinically important, or false negative results, which are statistically insignificant without excluding an important clinical effect[113]. Conversely, trials could be overpowered, leading to a waste of resources.

There is criticism of the use of mean or median change in group scores for patient-reported outcomes in clinical trials because it

oversimplifies complex outcomes in which some patients may improve and others deteriorate by different amounts. In order to overcome this difficulty, reporting of individual score change over time is advocated[114]. This requires an *a priori* responder definition based on the change in an individual patient score over time. The MID is the most appropriate value to use as this change in score because it represents a worthwhile change in the score. This can be used to determine the proportion of patients in each group that are responders.

Determining the MID for the VASD in patients with MPEs is important for my research, because this includes 2 clinical trials (TIME2 and TIME3-UK) assessing different treatments to relieve dyspnoea in patients with MPEs. In both of these trials, the primary outcome measure is the mean VASD. Knowledge of the MID for the VASD is essential for interpreting the results of these trials.

The MID may be useful for treating individuals in order to advise them on whether to undergo a specific treatment or whether to continue treatment, although clinicians should be aware that the MID may vary from person to person, based on their attitude towards the risks and benefits of the treatment.

2.1.3 Methods for calculating the MID

There are 3 major categories of approaches to determining the MID which I will discuss below[115]:

- Anchor (external measure);
- Opinion; and
- Distribution (statistical).

These approaches all have relative advantages and disadvantages and so for this study I have elected to use a combination of approaches.

2.1.3.1 Anchor methods

The anchor approach compares changes between the 'anchor' for which the MID is established, with a second tool, in order to determine the MID for the second tool. Many different anchors have been used. These can be other patient reported outcome measures such as a Likert scale, clinician ratings or direct clinical anchors.

For the primary outcome measure of this study, the anchor I have chosen to use is a 7 point Likert scale, which consists of the following options for patients to chose:

1. Large or moderate improvement;
2. Small but just worthwhile improvement;
3. Slight improvement but not worthwhile;
4. No change;
5. Slight deterioration but not significant;
6. Small but significant deterioration; and
7. Large or moderate deterioration.

Using this Likert scale as the anchor, the MID for the VASD will be determined from those patients responding that they have experienced a 'small but just worthwhile improvement'. Of note, the just noticeable difference studied by other researchers is equivalent to 'slight improvement but not worthwhile/slight deterioration but not significant', and clearly different from the MID. This method has the advantage that the VASD in patients experiencing a change equivalent to the MID can

be easily identified. For this reason, this is the main method that I will be using in this study to determine the MID for the VASD in patients with MPEs.

An alternative anchor method to a Likert scale is to use a second tool for which the MID has previously been determined e.g. Ries et al. compare the Shortness of Breath questionnaire with the Transition Dyspnoea Index[116]. This approach is only valid if the MID for the anchor measurement has been determined reliably and the two tools are measuring the same outcome. I use this method in this study to compare the change in VASD with change in the dyspnoea component of the Chronic Respiratory Disease Questionnaire (CRDQ). The CRDQ assesses dyspnoea over the previous 2 weeks and has been shown to be valid and reliable in patients with chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD)[117]. When completing the CRDQ, patients rate their dyspnoea over the previous 2 weeks during 5 different self-selected activities from 1 (maximum impairment) to 7 (no impairment). Patients recruited to TIME2 completed both the CRDQ and VASD as part of their follow up. The MID for the dyspnoea subsection of the CRDQ has been determined to be 0.5 using anchor-based approaches compared with global ratings of change[111, 118-120]. The CRDQ asks patients about their dyspnoea over the previous 2 weeks whereas the VASD is a measurement over the previous 24 hours. In the first 6 weeks of TIME2, patients completed a daily VAS diary and completed the CRDQ at 2, 4 and 6 weeks. Therefore I will compare the results of the CRDQ with the mean daily VASD over the previous 2 weeks.

An alternative approach for determining the MID is to use a non-patient related outcome as the anchor to map changes in the measure of interest to e.g. Karras et al. mapped changes in VASD in patients presenting with acute asthma to peak expiratory flow [121]. This method is not possible to determine the MID for the VASD in patients with MPEs because there are no equivalent objective measures in MPEs which can be used to map changes to. Although there is likely to be a correlation between decrease in size of effusion on CXR/US, volume drained, and change in VASD, this has never been studied systematically, and the MID for change in CXR appearance or volume of pleural fluid drained has not been determined.

Some previous studies have used as the anchor an intervention that is known to produce a small clinical benefit, such as pulmonary rehabilitation[116]. The researchers have made the assumption that this intervention is known to cause a modest improvement in symptoms, therefore the improvement in symptoms must be the MID. However, this approach is flawed because of this circular argument.

There needs to be a reasonable correlation between the anchor and the tool being assessed for this method to work, although what is represented by a 'reasonable correlation' is open to interpretation. R values of 0.5 and 0.30-0.35 have been suggested as a correlation threshold above which there is an acceptable association between the anchor and the second tool [122, 123]. An R value of 0.5 is the most commonly used value and was used in this study.

The methods described above represent longitudinal anchor methods for determining the MID based on changes in clinical state. Cross-sectional studies can also be performed, looking at differences between predefined groups of patients, but there are no appropriate ways to divide patients with MPEs to determine the MID using this method.

2.1.3.2 Opinion methods

The simplest and quickest method to determine the MID for a particular tool is to ask patients or health professionals what they consider to be the MID. In this study, patients will be asked what they consider to be the smallest worthwhile decrease in their breathlessness for the procedure they are about to undergo and this change will represent the MID. A limitation of using this method with patients is that the concept of the MID is not a simple one to grasp so may be difficult for patients to make this assessment. An additional limitation is that patients may not have a clear understanding of what the procedure entails until afterwards.

Health professionals have also been interviewed to assess what they consider to be the MID. Guyatt et al. considered that 'clinicians, through repeated use of the instrument in the clinical setting… develop an intuitive sense of the change in score that constitutes a minimal important difference'[124]. The Delphi method and consensus debate can be used to formalise this process[125]. However, it is difficult for clinicians who may have never experienced a symptom to assess what an important difference is. Although clinicians are able come to a

consensus for an estimation of the MID through these methods, this may not be similar to the value derived by other methods[125].

2.1.3.3 Distribution-based methods

Distribution-based or statistical methods aim to determine the MID based on the variation within the sample. Within this subset of methods for determining the MID, there are again multiple methods. These methods have been devised by looking at the distribution of values in tools for which the MID has previously been determined by anchor methods and attempting to find a common statistical formula which can predict these values.

Firstly, the standard error of measurement (SEM) is defined as the "variability between an individual's observed score and the true score" and is calculated as shown in Equation 2-1, where σ is the SD and *r* is the reliability coefficient. One SEM is thought to approximate the MID[126, 127].

Equation 2-1: Standard error of measurement

$$SEM = \sigma\sqrt{1-r}$$

The reliability coefficient can be measured using internal consistency (Cronbach's alpha) or test-retest methods. In this study, I calculate *r* using the test-retest method, in which it is equal to the correlation between the 2 measurements. Cronbach's alpha is not suitable for determining the MID in the VASD because it is a measure of internal consistency in outcome measures consisting of multiple categories.

The effect size (ES) index, as defined in Equation 2-2, where Δ is the difference in means and σ is the pooled standard deviation, is another statistical method used to estimate the MID. It has been mainly used by social scientists to judge the clinical importance of interventions. Small, medium and large treatment effects correlate with effect size indices of 0.2, 0.5 and 0.8 respectively[113]. A medium treatment effect size is generally considered to be approximately equivalent to the MID although other researchers have considered an effect size of 0.33 to be equivalent to the MID[128]. For this study, I will use a value of 0.5 to equate to the MID. A limitation of this approach is that if there is greater variability within a sample then there will a greater SD and hence the MID may be inappropriately small.

Equation 2-2: Effect size

$$ES = \frac{\Delta_x}{\sigma_x}$$

Finally, Sloan et al. proposed a distribution-based method called the empirical rule effect size (ERES)[129]. This method was developed to avoid the need to estimate the SD. Sloan assumes that quality of life scores are normally distributed and that the mean is a score of half the maximum value. Based on the empirical rule from statistics which states that approximately 99% of any normal distribution will fall within 3 standard deviations of the mean, the assumption is made that the theoretical range of any quality of life instrument (in the case of the VASD, 0-100mm) represents six SDs. Therefore an estimate of the SD for the VASD is 100/6 or approximately 17. Based on other methods

that demonstrate the MID to be equivalent to ½ the standard deviation, Sloan concluded that the MID for 100 point scales, including the VASD, is 8.4.

These distribution based methods have been criticised for not necessarily being linked to anything clinically meaningful and that the values obtained may not represent a minimal change[122]. The cut-offs chosen are arbitrary and there is disagreement over what values to chose. However, they are a useful substitute for anchor methods if these are not available.

2.1.3.4 Triangulation of results for the MID

Using multiple methods for determining the MID will lead to multiple results. Some authors advocate the use of triangulation to resolve this dilemma[125]. This may overcome bias generated by using a single methodology and enable a more accurate result. However, it may not be appropriate to combine different approaches, especially if they were determined in different patient groups or based on different interventions. Researchers may need to accept that there is not a single convenient MID for each measuring tool, but rather that MID varies with treatment, context and patient group and is a range rather than a single value.

2.1.4 Factors influencing the MID

Although it has always been recognised that the MID varies between tools, it has traditionally been thought of to be a single value for an individual tool. However, it is increasingly being recognised that

there are many factors influencing the MID for a particular tool, such as the disease, treatment and individual patient.

2.1.4.1 Type of pleural procedure

A patient's estimation of whether a treatment is 'worthwhile' is a trade off between the benefit, side effects and inconvenience of the treatment, therefore the MID is likely to be greater for more invasive pleural procedures that require an inpatient stay compared to less invasive day case procedures. I studied this possibility in this project, by analysing patients' opinion of the MID separately, depending on the procedure the patients were undergoing. The procedures included in this study are:

- **Diagnostic aspiration**: this involves aspiration of a small volume of pleural fluid only (typically 60ml) and would not be expected to produce much change in symptoms. This is an outpatient procedure and is very low risk.
- **Therapeutic aspiration**: this involves large volume drainage of pleural fluid only. A maximum volume of 1500ml is recommended for this procedure due to the risk of reexpansion pulmonary oedema but less may be drained, because the patient may have less fluid than this in their pleural space or the procedure may be halted early due to cough or chest tightness[1, 130]. This is an outpatient procedure and is low risk.
- **Chest drain and pleurodesis**: this involves drainage of the entire volume of pleural fluid as an inpatient followed by talc pleurodesis. Average length of hospital stay is 4 days[131]. Usually, when the

post-procedure VASD was performed, the patient has drained the pleural effusion but not undergone pleurodesis. This procedure carries a low risk of infection, bleeding and organ damage.

- **Indwelling pleural catheter (IPC) insertion and drainage**: this involves outpatient insertion of an IPC followed by large volume drainage of most but not all of the pleural effusion. This procedure carries a low risk of infection, bleeding and organ damage, but there is a significant long-term risk of complications of the IPC.
- **IPC drainage**: this procedure involves outpatient drainage of up to 600ml of pleural fluid from an IPC and does not involve significant risk.
- **Local anaesthetic thoracoscopy**: this procedure involves drainage of the entire volume of pleural fluid under sedation followed by pleural biopsies and/or pleurodesis during the same procedure. Patients undergoing pleurodesis would be admitted to hospital for an average of 2 days but other patients are treated as day cases. A short term effect of the pleurodesis may be dyspnoea. This procedure carries a small but significant risk of infection, bleeding and organ damage.

2.1.4.2 Magnitude of the initial symptoms

There is some data suggesting the MID depends on the magnitude of the initial symptoms. Ander et al. found that patients with a low initial level of dyspnoea (initial VASD 0-50mm) considered a mean change in VAS of 5.7mm (95% confidence interval -3.6-15.0mm) to represent either ‘a little less difficulty breathing’ or ‘a little more difficulty breathing’ whereas for patients with a high initial VAS (51-100mm)

considered a mean change of 30.9mm (95% CI 19.1-42.6mm) to represent this [132]. However, this apparent dependency may be due to mathematical coupling, rather than a true dependency. Mathematical coupling occurs 'when one variable directly or indirectly contains the whole or part of another'[133]. Therefore Oldham's method will be used to assess if there is a true relationship between baseline VASD and MID. Oldham demonstrated that for two series of independent random numbers *x* and *y* with the same standard deviation, there is a strong correlation of approximately 0.71 between *x* (i.e. the baseline measurement) and *x*-*y* (i.e. the change in measurement). This has led to some researchers inappropriately concluding that there is a correlation between baseline score and change in score and therefore that the MID is dependent on baseline score. Oldham demonstrated that calculating the correlation between *x*-*y* and (*x*+y)/2 lead to a true assessment of the correlation between the variables. This is therefore an unbiased test of the relationship between baseline VASD and change in VASD.

2.1.4.3 Positive and negative changes

There is also some evidence that the MID can be different for a positive change in a scale than that for a negative change[134]. For this reason, I will only look at positive changes in the VASD in this study. Given that these procedures should improve breathlessness, there is unlikely to be sufficient evidence from this work to compare the MID for positive and negative changes.

2.1.5 Previous studies assessing the MID for the VASD

There have been few studies which have attempted to determine the MID for the VASD, and none of these studies have included patients with MPEs.

One previous review article retrospectively reviewed trials that used the VASD as an outcome measure to assess efficacy of various interventions: pulmonary rehabilitation, oxygen supplementation or lung volume reduction surgery[116]. The authors considered that these interventions would give small but clinically meaningful decreases in dyspnoea i.e. equivalent to the MID. The article was limited by the small number of studies which have used the VASD as an outcome measure. Of the studies they reviewed, two had a medium effect size which was associated with decrease in VASD of 12mm with effect size 0.48 in 1 study and decrease in VASD of 10mm with effect size 0.6 in a second study[135, 136]. They concluded that there were few studies with limited data and the MID could not be defined with precision based on the available data, but suggested that 'a change in VAS of approximately 10 to 20mm is associated with a modest level of symptom change in patients with chronic lung disease'[116].

Ander et al.[132] assessed the MID of the VASD in 79 patients presenting to the emergency department with decompensated heart failure using an anchor approach with a 5 point Likert scale. Patients assessed the change in their dyspnoea using both a VASD and 5 point Likert scale. In this study, the researchers equated the MID with 'a little

less difficulty breathing' or 'a little more difficulty breathing'. The value obtained was 21mm (95% CI 12-30mm). This value is slightly greater than the range suggested by Ries but there is overlap in the confidence intervals between the two.

Karras et al. found a decrease in VASD of 22mm (95% CI 11-34mm) to be the MID in 156 patients presenting to the emergency department with an exacerbation of asthma using the same technique as Ander et al. above[121].

Other researchers have assumed the MID for the VASD to be 10mm, but do not present a justification for the selection of this value[116, 136, 137].

These papers suggest a range of estimates for the MID VASD. This demonstrates that there is a need for further research to determine the MID for the VASD, especially in patients with MPEs.

Of note, all these estimates are greater than the delta value used in the power calculations for TIME2 and TIME3 (7mm), suggesting these studies may be overpowered. As discussed previously, the MID VASD may be different for different interventions and it is possible that the MID VASD may be lower for chest drain/IPC insertion than acute treatment of CCF or pulmonary rehabilitation but this is unlikely, given that these pleural procedures involve significant side effects and inconvenience to the patient.

2.1.6 Aims and hypotheses of this study

The main aim of this study was to use a combination of anchor, statistical and opinion methods to define the MID of VASD, analysing both data collected as part of the TIME2 and TIME3-UK clinical trials and new data collected specifically for this study. The primary method used to determine the MID was an anchor approach compared with a 7 point Likert scale. This method was chosen as the primary outcome as anchor methods are thought to be the most accurate method for determining the MID and the Likert scale is the best anchor available for the VASD in patients with MPEs.

Other outcomes in this study were:

- The influence of type of pleural procedure on MID: I hypothesise that more invasive pleural procedures, such as thoracoscopy, will have a greater MID than less invasive procedures, such as diagnostic aspiration.
- The relationship between change in VASD and volume of pleural fluid drained: I hypothesise that there will be a greater decrease in VASD when a greater volume of fluid is drained. This data may enable clinicians to identify a minimum volume of fluid that needs to be drained to give patients a worthwhile improvement in symptoms.
- The effect size for different pleural procedures: this data will provide data to compare the degree of improvement in VASD between different pleural procedures. I hypothesise that pleural procedures which result in a greater volume of fluid drained (i.e. thoracoscopy, indwelling pleural catheter (IPC) insertion and drainage, and chest

drain and pleurodesis) will have a greater effect size than procedures resulting in smaller volumes drained (i.e. diagnostic aspiration).

- The reliability and validity of the VASD for assessing patients with MPEs: the VASD has not previously been formally assessed for reliability and validity in this group of patients. Although determining reliability and validity of the VASD is not the prime aim of this study, I will be assessing test-retest reliability and responsiveness of the VASD to fluid drainage (i.e. its validity). Knowing that the VASD is valid and reliable is important if it is to be used in further clinical trials.

2.2 Methods

2.2.1 Study design

This study consisted of a questionnaire (Appendix A) administered to patients with a MPE prior to a pleural procedure performed at the Churchill Hospital, Oxford. The wording of the questionnaire was designed to be identical to that of the VASD diaries in the TIME2 and TIME3 trials, so that results would be applicable to these studies. Additionally, data that had been collected as part of the TIME2 and TIME3 trials, of which TIME2 is reported subsequently in this thesis, was analysed. The methods used to collect the TIME2 data are reported in Chapter 4 of this thesis.

2.2.2 Subject characteristics

2.2.2.1 Inclusion Criteria

Patients attending the Oxford Respiratory Unit with a confirmed or suspected malignant pleural effusion for a pleural procedure were eligible for inclusion in this study. The pleural procedures included were diagnostic and therapeutic aspiration, chest drain insertion, indwelling pleural catheter insertion and/or drainage and local anaesthetic thoracoscopy. Specific inclusion criteria were:

- Male or Female, aged 18 years or above;
- Diagnosed with pleural effusion using CXR or ultrasound;
- Attending the Oxford Respiratory Unit for a pleural procedure;
- Diagnosed with a MPE based on radiological evidence or positive histocytology or currently under investigation for a suspected MPE;
- Symptoms of dyspnoea.

2.2.2.2 Exclusion Criteria

The participant was not eligible to enter the study if either of the following applied:

- Unable to speak English;
- Unable to comply with the study protocol.

2.2.3 Data collection

Patients completed the questionnaire in Appendix A. The initial 2 questions were answered prior to the pleural procedure. These questions were:

1. baseline VASD and
2. the worthwhile decrease in VASD.

If patients did not understand question 2 initially ('What is the smallest decrease in your breathlessness that you would consider worthwhile for this treatment?'), I explained that the procedure involved coming into hospital and taking a small degree of risk so how much improvement in their breathing would they need to have to consider the improvement to be worthwhile this inconvenience and risk.

If the patient was an inpatient, I then visited them on the ward in order to complete the final 2 questions on the questionnaire approximately 24 hours later. If the patient was an outpatient, they were given the questionnaire to take home with a stamped addressed envelope and asked to complete the remaining questions approximately 24 hours later. These questions were:

3. post-procedure VASD and
4. 7 point Likert scale.

Additionally, the patient's date of birth, sex, diagnosis, procedure performed and volume of fluid drained in 24 hours were recorded.

2.2.3.1 Data collection in TIME3-UK trial

The TIME3-UK trial is a randomised trial comparing intrapleural urokinase with placebo for the treatment of patients with septated MPEs which are not draining despite the presence of a patent chest drain. For this study, patients were asked to complete 2 baseline VAS scores. One was completed immediately following consent and the second was completed immediately prior to administration of the first dose of drug. There was approximately 2 hours between these scores.

2.2.4 Statistical analysis

The statistical analysis plan was finalised prior to any assessment or analysis of data.

All patients on whom data was available were included in the analyses. All analysis were pre-planned prior to any data analysis unless specifically stated. SPSS version 20.0.0 was used. Data (VASD scores, CRDQ scores and volume of fluid) were assessed for normality prior to further analysis.

2.2.5 Primary outcome

The primary outcome of this study is the mean change in VASD of subjects reporting they experienced a 'small but just worthwhile improvement' in their dyspnoea after the pleural procedure. This value is an estimation of the MID of the VASD calculated using the anchor method (by comparing to a 7-point Likert scale).

Patients were categorised based on their response to the 7 point Likert scale. The mean decrease in VASD (question 1 – question 3) was

calculated for each group. ANOVA was used to determine whether the mean decrease in VASD for the group responding 'small but just worthwhile improvement' is significantly different from the other groups. Additionally, 95% CIs were calculated.

2.2.6 Secondary outcomes: alternative methods for determining the MID

2.2.6.1 Anchor methods for determining MID: analysis of TIME2 data compared with CRDQ dyspnoea domain

The mean VASD over 2 weeks was calculated and compared with the score of the dyspnoea domain of the CRDQ assessed over the same time period. Only patients with 'semi-complete' data for the VASD were included in this analysis i.e. at least 12 of 14 possible measurements. The correlation between mean VASD and CRDQ dyspnoea domain was determined and the change in mean VASD equivalent to a 0.5 change in the CRDQ dyspnoea domain was calculated.

2.2.6.2 Opinion methods for determining MID

This was calculated as the mean result of question 1 – question 2. Again, 95% CI were calculated.

2.2.6.3 Distribution-based methods for determining MID

2.2.6.3.1 Standard error of measurement

This was calculated using baseline data from the TIME3-UK trial in which patients completed paired baseline VASD scores using Equation

2-1 above. The reliability coefficient was calculated as the correlation (*r*) between the two scores.

2.2.6.3.2 Effect size index

An effect size of 0.5 is thought to represent the MID. Effect size is calculated using Equation 2-1. Therefore the MID was calculated as half the SD of the baseline VASD scores (question 1).

2.2.7 Secondary outcomes: other analyses

2.2.7.1 MID in subset of patients with confirmed MPE

Patients undergoing investigation for possible MPE were included in this study. Some of these turned out subsequently to have benign disease. This analysis was performed as described for the primary outcome above but only including the subset of patients who were confirmed to have MPE.

2.2.7.2 MID for individual pleural procedures

Subjects were divided based on the pleural procedure they underwent (diagnostic aspiration, therapeutic aspiration, chest drain insertion, indwelling pleural catheter insertion and medical thoracoscopy). The MID was calculated as described for the opinion data above in each subgroup and one-way ANOVA used to determine whether patients considered the MID to be different for different procedures.

2.2.7.3 Assessing the relationship between baseline VASD and change in VASD

This will be assessed based on Oldham's method by determining the correlation between the decrease in VASD (i.e. x-y) and the mean of the pre- and post- procedure VASD (i.e. $(x+y)/2$).

2.2.7.4 Correlation between volume of fluid drained and decrease in VASD

The correlation between volume of fluid drained and decrease in VASD was calculated, using Pearson's rank correlation coefficient. The volume of fluid drained corresponding to a change in VASD equal to the MID will be calculated.

2.2.7.5 Effect size of different pleural procedures

The effect size of decrease in VASD following different pleural procedures (aspiration, chest drain etc) will be calculated using Equation 2-2.

2.3 Results

2.3.1 Demographics

A total of 104 questionnaires were completed. Average age was 70 years (data available on 97 questionnaires). Fifty-five (56%) of 98 patients with data on gender available were female. Diagnoses are summarised in Table 2-1. Number of different procedures are summarised in Table 2-2. Average volume of pleural fluid drained within 24 hours was 1200ml. For inpatients, completion rate of the second part

of the questionnaire was 96%. For outpatients, 88% of questionnaires were returned.

Table 2-1: Underlying diagnosis

Diagnosis	Number of patients
Breast cancer	33
Mesothelioma	20
Non-small cell lung cancer	16
Ovarian cancer	4
Leiomyosarcoma	2
Colorectal cancer	3
Carcinoma of unknown primary	1
Chondrosarcoma	1
Transitional cell carcinoma of the bladder	1
Benign pleural effusion	14
Undiagnosed	1
Not recorded	6

Table 2-2: Number of different pleural procedures

Procedure	Number of patients
Chest drain	13
Diagnostic tap	10
IPC drainage	1
IPC insertion and drainage	10
Therapeutic aspiration	33
Thoracoscopy	29
Not recorded	6

All continuous data was found to be normally distributed.

2.3.2 Primary outcome

Data was available in 95 patients. Data on number of patients, mean decrease in VASD and 95% CI based on change on Likert scale is summarised in Table 2-3. The mean decrease in VASD for patients experiencing a 'small but just worthwhile improvement' was 22mm (SD 13mm, 95% CI 16-27mm). There was a statistically significant difference between groups as determined by one-way ANOVA ($F(5,89)=26$,$p<0.001$). A Tukey post-hoc test revealed that the VASD was significantly lower in the 'small but just worthwhile improvement' compared to the 'large or moderate improvement' group (mean difference 21mm, 95% CI 31-11mm, $p<0.001$). There was no significant difference between the VASD in the patients experiencing a 'small but just worthwhile improvement' compared to 'slight improvement but not worthwhile' (mean difference 5.4mm, 95% CI -14 - 23mm, $p=0.94$).

Table 2-3: Summary of decrease in VASD categorised by response on Likert scale

Likert scale	No. of patients	Decrease in VASD (mm)	SD (mm)	95% CI (mm)
Large or moderate improvement	54	43	15	39 - 47
Small but just worthwhile improvement	23	22	13	16 – 27
Slight improvement but not worthwhile	5	16	14	-1.2 - 34
No change	8	10	14	-1.2 - 22
Slight deterioration but not significant	4	-6.4	9.8	-22 – 9.3
Small but significant deterioration	0	N/A	N/A	N/A
Large or moderate deterioration	1	-56	N/A	N/A

Table 2-4: Summary of estimates of MID

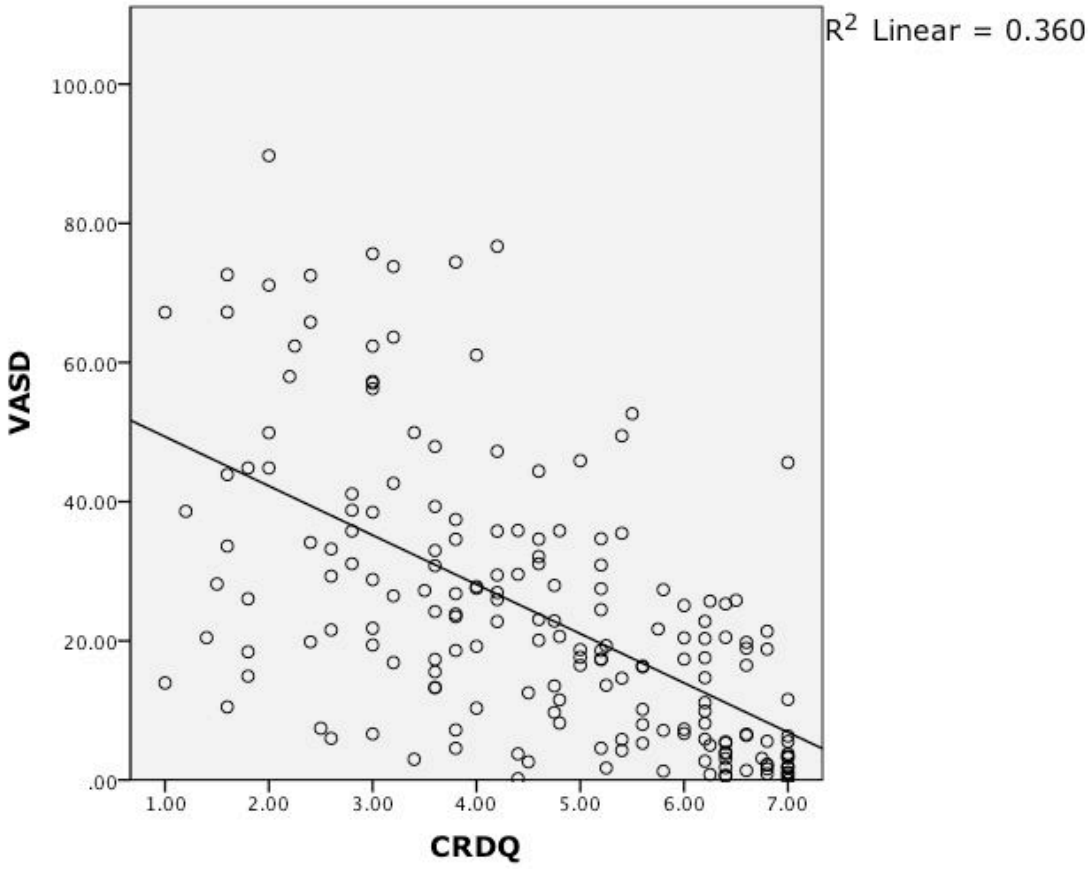
Method	Result (mm) (95% CI)
Anchor methods	
With Likert scale	22 (16 – 27)
Comparison with CRDQ dyspnoea domain	3.5 (2.9 – 4.2)
Opinion method	24 (20 - 27)
Statistical methods	
Effect size index	12
Standard error of measurement	6.4
Empirical rule effect size	8.4
Other studies	
Ander et al.[132]	21 (12-30)
Karras et al.[121]	22 (11-34)

2.3.3 Secondary outcomes: alternative methods for determining the MID

2.3.3.1 Anchor methods for determining MID: analysis of TIME2 data compared with CRDQ dyspnoea domain

For this analysis, 190 data points were available. Correlation between CRDQ and mean VASD was -0.60 ($p<0.001$). Data is summarised in Figure 2-1. The change in mean VASD equivalent to a 0.5 change in the dyspnoea domain of the CRDQ was 3.5mm (95% CI 2.9 - 4.2).

Figure 2-1: Scatter plot of CRDQ and VASD data



A post-hoc analysis was carried out to see if a correlation with greater weighting on later VASD scores (doubled weighting for the second week of scores) had a better correlation with the CRDQ result. Correlation between CRDQ and mean VASD on this weighted analysis was -0.61 ($p<0.001$). No further analysis was carried out on this weighted data.

A further post-hoc analysis was carried out to see if the within patient correlation change in CRDQ and change in mean VASD provided a better approximation for the MID. 100 sets of paired measurements were available for analysis. The correlation was in fact worse (-0.27, $p=0.007$) and the correlation coefficient was only -2.2, suggesting a value for the MID of only 1.1mm.

2.3.3.2 Opinion based method for determining the MID

The mean decrease in VASD that patients considered to be worthwhile for the treatment they were undergoing was 24mm (95% CI 21 - 27mm). Of note, this concept was difficult for patients to grasp, and common responses to this question were 'Any improvement would be worthwhile' and 'This is where I want to be' (indicating 0mm/'not breathless at all').

2.3.3.3 Distribution-based methods for determining the MID

2.3.3.3.1 Standard error of measurement

Paired VASD scores were available on 32 patients enrolled in the TIME3 trial. One of these patients was not included in the analysis because it was clear from the patient's comment ('breathing much better after second dose of drug') that the second score was not a baseline score. Mean VASD for the first score was 37mm (SD 30mm) and for the second score was 33mm (SD 27mm). This difference was statistically significant (95% CI 1.2 – 8.3mm, p=0.010). The correlation between the two measurements was 0.95. The overall SD for the VASD scores was 28mm. The standard error of the measurement was calculated to be 6.4mm.

2.3.3.3.2 Effect size index

The SD of pre-procedure VASD scores was 23mm, therefore, based on a ES of 0.5, the MID is 12mm.

2.3.4 Secondary outcomes: other analyses

2.3.4.1 MID in subset of patients with confirmed MPE

Of the patients included in the study, 81 patients had confirmed cancer. Within this group of patients, the MID calculated as in the primary outcome was 20mm (95% CI 14 - 26mm).

2.3.4.2 MID for individual pleural procedures

One-way ANOVA showed no differences in the MID for the VASD (opinion method) based on type of procedure ($F(5,89)=1.5$, $p=0.20$). Given the number of different procedures and different possible responses on the Likert scale, there was insufficient data to accurately calculate the MID for each procedure using the same method as for the primary outcome.

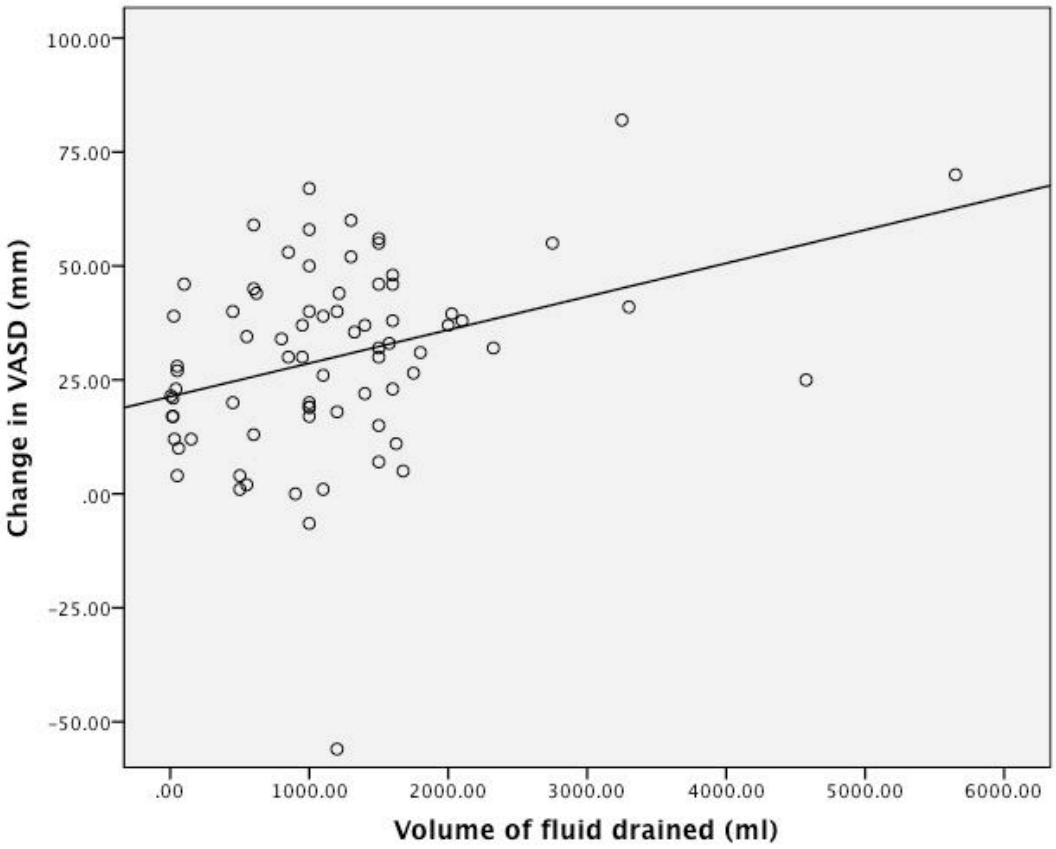
2.3.4.3 Correlation between initial VASD and decrease in VASD

There was a significant correlation between the initial VASD and the decrease in VASD following a pleural procedure ($r=0.60$, $p<0.001$). However, using Oldham's method (i.e. calculating the correlation between change in measurement and mean of baseline and second measurements as described in section 2.2.7.3) to correct for the problem of mathematical coupling, it was demonstrated that there was no true correlation between initial VASD and decrease in VASD ($r=0.13$, $p=0.21$).

2.3.4.4 Correlation between volume of fluid drained and decrease in VASD

Paired data on volume of fluid drained and decrease in VASD was available in 75 patients. There is a weak but significant correlation between the volume of fluid drained and the change in VASD (r=0.34, p=0.003) (Figure 2-2). Based on this calculation, the volume of fluid needed to be drained in order to produce a change in VASD of 22mm (i.e. in order to give a patient a change in symptoms equivalent to the MID) is 460ml.

Figure 2-2: Correlation between volume of fluid drained and decrease in VASD



2.3.4.5 Effect size of different pleural procedures

Effect sizes calculated as in Equation 2-2 using VASD following different pleural procedures are summarised in Table 2-5.

Table 2-5: Effect size for different pleural procedures

Procedure	**Mean decrease in VASD (mm)**	**SD (mm)**	**Effect size**
Chest drain	25	9.6	2.6
IPC insertion and drainage	34	19	1.8
Therapeutic aspiration	22	12	1.8
Diagnostic aspiration	20	11	1.8
Thoracoscopy	24	15	1.6

2.4 Discussion

2.4.1 Primary outcome

The primary outcome for this study was the change in VASD corresponding to a 'small but just worthwhile improvement' on the Likert scale in dyspnoea and was found to be 22mm (95% CI 16 – 27mm). This value is very similar to the values found by previous studies (Table 2-4) which have assessed the VASD in a similar way despite the fact that these studies assessed the MID in different groups of patients and treatments (patients with heart failure treated with diuretics and

asthmatics treated with salbutamol and steroids) and in a different setting (emergency department)[121, 132]. It may be that the MID for acutely dyspnoeic patients in a hospital setting is similar across different conditions. A similar value was found when just assessing patients with confirmed MPE.

This value of 22mm (95% CI 16 – 27mm) is much greater than the value that previous experts have assumed the MID to be (10mm)[116, 136]. The data here suggests that clinicians assume smaller changes in symptoms on the VASD to be worthwhile compared to patients' views. When the power calculations for TIME2 and TIME3-UK were performed, the delta value chosen was 7mm, a value that was considered by our research group at the time to represent the MID. This work shows this value was underestimated.

A limitation of this data is that the majority of patients experienced a 'large or moderate improvement' and very few experienced a 'slight improvement but not worthwhile', no change in their symptoms or a deterioration in their symptoms. It is therefore difficult to accurately determine the change in VASD for these categories and differentiate them from the MID. Collection of further data would help with this problem to a degree, but a huge number of patients would have to be surveyed to collect enough data.

The mean change in VASD in patients experiencing 'no change' in their symptoms was 10mm (95% CI -1.2 – 22mm), rather than 0mm, although the 95% CI did cross zero. This result is odd, especially because patients could see their pre-procedure VASD when completing

their post-procedure VASD. This result may be due to intrinsic error in the VASD, lack of understanding and due to the small numbers involved.

This method for determining the MID has been criticised because the Likert scale requires patients to think back to a previous level of dyspnoea and this may be influenced by the patient's current health status[128]. However, in this study, there was only 24 hours between the 2 assessments, so this issue is less of a problem for this study.

Patients were able to see their pre-procedure VASD when assessing their post-procedure VASD. This method was chosen because patients completing the VASD diary for TIME2 and TIME3-UK were able to see previous VASD scores. Additionally, there is evidence that letting subjects see their previous responses increases the validity of patient-reported outcomes[138].

2.4.2 Secondary outcomes: other methods for determining the MID

2.4.2.1 Data analysis of TIME2 data: anchor method comparing with CRDQ dyspnoea domain

The VASD data from TIME2 compared with paired CRDQ values produced an MID which was much smaller than the values produced from other analyses and from results seen in other studies and intuitively seems too small to be a true estimate for the MID. This is likely to be because the CRDQ is a less sensitive measure of large changes in dyspnoea than the VASD.

If we assume that maximum dyspnoea measured on the VASD (100mm) is equivalent to a maximum dyspnoea measured on the dyspnoea domain of the CRDQ (score of 1) and no dyspnoea on the VASD (0mm) is equivalent to no dyspnoea during the activities assessed in the dyspnoea domain of the CRDQ (score of 7) and there is a linear relationship between the two, then a change of 0.5 on the CRDQ would be equivalent to a change of 8.4mm on the VASD. However, this study found a change of 0.5 on the CRDQ was equivalent to a change of only 3.5mm on the VASD, suggesting that the CRDQ is insensitive to changes in the VASD.

The CRDQ was originally designed to measure small changes in dyspnoea in patients with chronic respiratory disease such as chronic obstructive pulmonary disease (COPD). When the patients first complete the questionnaire, patients chose 5 activities which are important to them which are currently making them breathless e.g. showering, shopping. They then chose an option on a 7-point Likert scale corresponding to how breathless they have felt over the previous 2 weeks doing that activity. This is ideal for detecting small differences in dyspnoea.

The CRDQ has never been validated in patients with MPEs. These patients experience much greater variation in breathlessness than patients with COPD: they experience a large improvement following large volume drainage of their pleural effusion; and a large deterioration as their cancer progresses or their pleural fluid reaccumulates. This means that they may experience no breathlessness at all doing the original activities they chose for the questionnaire and also be able to

run without breathlessness, but the CRDQ is unable to assess this greater improvement in breathlessness. Equally, the patient may be so breathless that they have not been able to do an activity for the last 2 weeks, in which case they have not answered this item in the questionnaire. Analysis of the CRDQ ignores this and inputs an mean value for unanswered questions. This means the CRDQ is insensitive to large changes in breathlessness.

Although there is disagreement between the degree of correlation between an anchor and tool, the correlation between the CRDQ and the mean VASD was 0.60, which is greater than the most conservative value for *r* proposed[123]. Therefore, poor correlation between the CRDQ and VASD is not likely to be the reason why the value obtained for the MID was different from the other methods used.

These limitations of the CRDQ suggest that it is insensitive to changes in dyspnoea in patients with MPEs. Therefore, the low value obtained for the MID using this method is likely to be due to limitations in the CRDQ in this patient population, rather than a true result. These results suggest that the CRDQ should not be used to assess dyspnoea in patients with MPEs.

2.4.2.2 Opinion method

The decrease in VASD the patients considered to be worthwhile for the procedure they were having i.e. the MID was 24mm (95% CI 21 - 27mm), a value which is very close to the value determined by the anchor method. The similarity between these values strengthens the argument that 22mm is a good estimate of the MID for the VASD.

However, patients did find this question difficult to comprehend and answer, although all patients did answer.

2.4.2.3 Statistical methods

The statistical methods used in this study all give a lower value than that obtained from patients. These methods all have limitations. The standard error of the measurement gives a very low value due to the high test-retest correlation for the VASD. One factor confounding this result in the TIME3 data used is that patients were able to see their first response when they answered the second VASD. This was done deliberately because, in the VAS diaries the patients complete, they are able to see the previous response and compare them directly. The correlation may have been lower if patients were blinded to their previous result, thereby giving a greater value for the MID.

The ES index also gave a lower value for the estimation of the VASD, perhaps because an effect size of 0.5 is too low an effect size to approximate the MID for procedures with significant inconvenience and risk.

The empirical rule effect size (ERES) is based on assumptions that are invalid in this data set. It assumes the mean is 50% and the SD is 16.7, neither of which are the case. Therefore 8.4mm is not a reasonable estimate of the MID. It is clear that the MID varies between diseases, treatments and populations and the ERES is not sensitive to these variations.

Statistical methods for determining the MID are criticised for demonstrating a clinically significant and meaningful change, but not a

minimal one[122]. It is therefore interesting that the values determined by the statistical methods are smaller than that derived from the Likert anchor method. This may be because these methods do not take into account the risks of a treatment. Pleural interventions involve a greater risk and inconvenience to the patient than other treatments and therefore distribution based approaches to estimating the MID do not appear to be appropriate.

Statistical methods for calculating the MID should be considered supportive of anchor-based approaches, or used only when there are no better data available. Since these estimates are not close to the anchor estimation for the VASD, these approximations should not be considered to related to the true MID.

2.4.3 Secondary outcomes: further analyses

No difference was found for patients' estimates of the MID based on the different pleural procedures. This may be because patients do not consider these procedures to be very different prior to having the procedure, because they may not have a very clear idea of the relative risks and inconveniences of the different procedures.

Statistical analysis using Oldham's method showed no true correlation between baseline VASD and decrease in VASD, demonstrating that the MID is a constant, regardless of the patient's baseline breathlessness. This result makes planning and analysing studies much simpler.

Results showed a weak correlation between volume of fluid drained and decrease in VASD, suggesting that a minimum drainage of

460ml of pleural fluid would give patients a worthwhile improvement in VASD. However, the weak correlation between these variables means that this data can not be used to guide treatment of individual patients. Many other factors, such as inversion of the diaphragm and response to pleurodesis, also affect the change in VASD in individual patients.

Effect size varied slightly for different pleural procedures, although the accuracy of these results is limited by the small numbers of procedures in some categories. The ES for diagnostic aspiration was surprisingly large (1.8), given the small volume of fluid aspirated, and this may be due to a placebo effect. The ES for LAT was surprisingly small (1.6) compared to the other procedures given that the entire pleural effusion is drained during the procedure. The ES for LAT may be smaller than expected due to acute dyspnoea caused by pleurodesis and on-going pleuritic pain due to the presence of a chest drain. Over the longer term, I would expect the ES to be greater for LAT because the majority of patient have a successful pleurodesis. All the values for the ES obtained were greater than 0.8, a value considered to be a 'large' effect and this is unsurprising given the very large improvements in dyspnoea noted clinically following a pleural procedure.

2.4.4 A single value for the MID?

When commencing this study, the plan was to use triangulation of the values obtained through these different methods in order to obtain a more accurate estimation of the MID. However, given the large difference between the measurements and the limitations discussed above, the data suggests that this would not be a valid approach.

The definition of MID which I chose to use was a patient centred one, and therefore the primary outcome is likely to be the one that most closely estimates the true MID. Experts in the field recommend that estimates of the MID are based primarily on patient determined anchors[122].

One limitation of the estimate of the MID obtained in this study is that it is context specific, so it may only represent the MID in patients with MPEs and not be applicable to other patient groups. However, the values obtained are similar to those found in patients in the emergency department with acute dyspnoea secondary to heart failure and asthma so may be more widely applicable[121, 132].

Another assumption commonly made is that MID values apply to individuals as well as populations. This data shows that there is variation in what patients consider to be the MID. It is recommended that patients in trials are classified as responders or non-responders based on the mean MID in a population. The fact that MID varies between individuals may mean that patients who consider themselves to have benefitted are classified as non-responders in a trial and *vice versa*.

This data suggests that there is not a single value for the MID of the VASD, but that 22mm is a good approximation of it in patients with MPEs undergoing pleural procedures.

2.4.5 Implications for TIME2 and TIME3-UK

When the sample size was calculated for both TIME2 and TIME3, the delta value chosen was 7mm, based on pilot data showing a difference of 7mm in VASD between patients treated with IPC and those

treated with chest drain. If the power calculation for both studies is repeated using 22mm as the value for delta and 19mm for the SD (which was the SD for the mean VASD in TIME2) with 90% power and α 0.05, then the sample size (including an additional 25% to allow for potential loss to follow up) would have only been 40 subjects compared to an actual sample size of 106 in TIME2 and 126 in TIME3. A more conservative estimation of the sample size required, using the lower end of the 95% CI (16mm) calculated as above is 75 subjects.

2.4.6 Use of VASD for assessment of dyspnoea in patients with MPEs

As well as providing data to determine an MID for the VASD, this study helps to validate the use of the VASD in patients with MPEs. It shows that it is simple to administer, easily understood by patients and acceptable. It demonstrated that it has construct validity because results on the VASD are responsive to pleural interventions and, as clinicians would expect, are correlated with volume of pleural fluid drained.

2.5 Conclusion

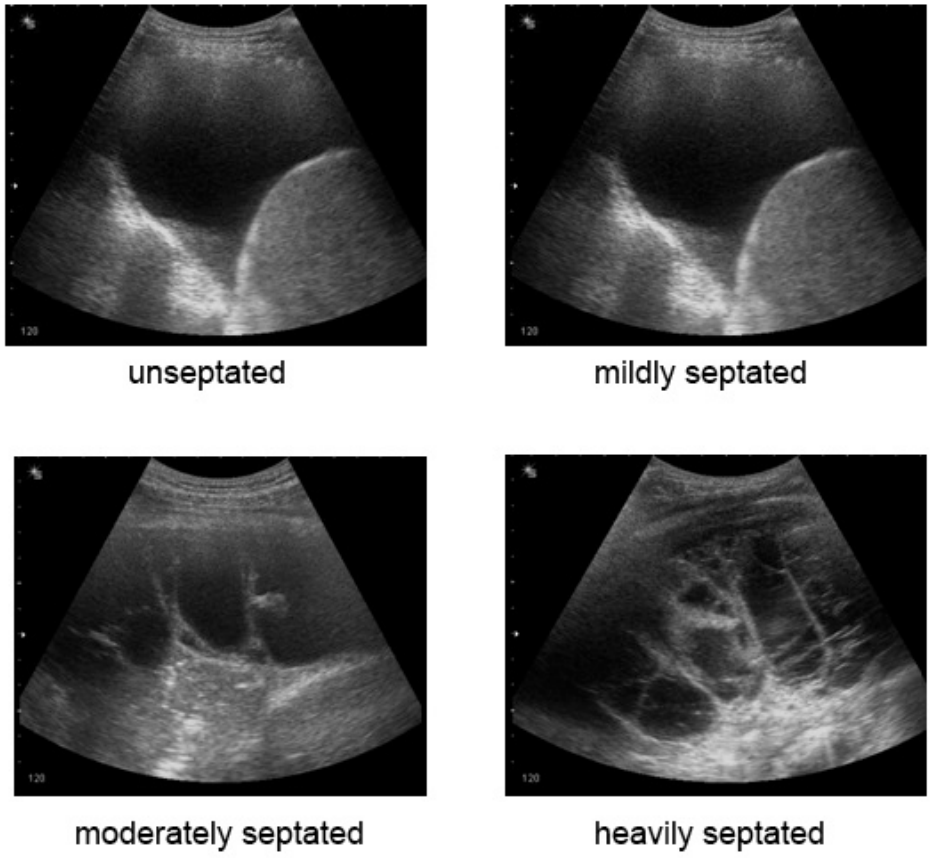
The best estimate for the MID for the VASD in patients with MPE obtained in this study was 22mm (95% CI 16 – 27mm), using an anchor based approach compared to a Likert scale. This value should be used to determine sample size in future RCTs and help interpret the results of TIME2 and TIME3-UK.

3 Development of a thoracic ultrasound septation score for pleural effusions

3.1 Introduction

This chapter describes the development of an objective thoracic ultrasound septation score (TUSS) to enable clinicians and researchers to reliably assess the degree of septation of pleural effusions. Thoracic ultrasonographers commonly categorise pleural effusions as unseptated, mildly, moderately or heavily septated (Figure 3-1).

Figure 3-1: Ultrasonographic appearances of unseptated, mildly, moderately and heavily septated effusions



This is a subjective judgment and the TUSS represents an attempt to objectify this assessment in order to develop a useful tool to predict clinical outcomes and help guide patient management.

3.1.1 Research applications

The fourth project included in the work of this research fellowship, but not reported in this thesis because recruitment is still underway, is an RCT assessing the effect of an intrapleural fibrinolytic (urokinase) in MPEs which are not draining despite the presence of a patent chest drain (TIME3-UK). It is likely that these effusions are not draining due to the presence of septations, fibrinous sheets which divide the effusion into multiple pockets of fluid. TIME3-UK is assessing the hypothesis that urokinase will break down these fibrinous sheets, allowing better drainage of the pleural effusion, resulting in greater likelihood of a successful pleurodesis and improved symptom relief. Development of an objective TUSS is a key part of TIME3-UK, which will enable objective assessment of the degree of septations in the subjects included in this trial. It will also be important when clinicians put the results of this trial into practice.

A TUSS will also have applications in patients with septated pleural effusions due to other causes, such as pleural infection. The ORTU is about to start recruiting to a prospective cohort study of patients with pleural infection and a TUSS will form part of this study. For this reason, it was decided to include patients with pleural effusions due to any cause in this study.

3.1.2 Clinical applications

Septated pleural effusions may be more difficult to drain[53]. In patients with malignancy, this may result in ongoing breathlessness and failure of pleurodesis. In patients with pleural infection, failure of complete drainage may lead to ongoing sepsis. Septated effusions may require intrapleural fibrinolytics, DNase or surgery to allow full drainage. Early identification of pleural effusions which will not drain using a TUSS may allow early institution of surgery or intrapleural therapy, which may lead to decreased length of hospital stay and improved outcomes.

Patients with an undiagnosed pleural effusion may require a local anaesthetic thoracoscopy (LAT) to investigate the cause of their effusion. It is possible that patients with septated effusions are less likely to have a successful LAT with a positive yield. A TUSS may help guide choice of investigation.

Another potential clinical application is in assessing patients with a non-draining indwelling pleural catheter (IPC), a tunnelled drain which allows domiciliary drainage of an effusion. This could be due to a blockage within the IPC itself or heavy septations within the pleural fluid. IPC blockage is managed with saline flushes whereas septations within the pleural fluid are treated with intrapleural fibrinolytics, but there is no evidence base for these treatments. A TUSS may be useful in clarifying what is causing the problem of a non-draining IPC and to prospectively evaluate optimal treatment of these different scenarios.

3.1.3 Previous studies of septated pleural effusions

Sonographic features of a pleural effusion have previously been categorized into anechoic, homogenously echogenic, complex non-septated and complex septated.[139] All complex septated effusions are exudates. However, complex septated pleural effusions have not previously been further classified using objective terms.

Ultrasound performed during injection of intrapleural fibrinolytics demonstrates dissolution of septations[140]. Intrapleural fibrinolytics increase drainage of pleural effusions and this is thought to be due to dissolution of fibrinous septations[109, 141].

There has been little research done on the outcome of patients with septated pleural effusions. One study has shown that patients with pleural infection whose effusion has the sonographic appearance of complex septation are less likely to drain their effusion successfully with a small-bore chest drain, are more likely to be admitted to intensive care and more likely to die from their infection[142]. The authors of this paper did not attempt to subclassify septated effusions, but it is possible that there is a graded risk, with more heavily septated effusions leading to a greater risk of surgery or death.

Medford et al. demonstrated that ultrasound prior to LAT can detect fibrous adhesions and reduce pleural space access failure[143]. Septations were not assessed in this study. Ravaglia et al. assessed success of LAT for patients with empyema based on whether the empyema was free flowing, multiloculated or organised (i.e. septated),

and found that it was successful in 85% of patients with free flowing fluid, 92% of patients with multiloculated fluid and only 50% of patients with organised effusion[144].

There is clearly a need for more research to be done studying the relationship between ultrasound appearance at presentation, clinical outcome and optimal treatment strategy and a TUSS is a key part of this.

3.1.4 Aim of this study

The primary aim of this project was to develop a reliable, objective and valid ultrasound septation score which can categorise effusions into unseptated, mildly, moderately and heavily septated. An iterative process was used as described in the methods section, including a prospective validation phase. The gold standard for categorising effusions in this study was the decision of an experienced thoracic ultrasonographer, because there is no other standard available to assess the degree of septation within an effusion. The phases of the study were:

1. Validation of subjective assessment of degree of septation: This phase was a retrospective analysis of ultrasound and clinical data to demonstrate that subclassification of pleural effusions based on degree of septation by ultrasound was correlated with clinically important outcomes.
2. Development and testing a standardised protocol for scanning a patients and determination of candidate factors to be included in the TUSS.

3. Assessment of interrater reliability and association of candidate factors for inclusion in the TUSS compared with assessment by an experienced ultrasonographer in order to determine the factors to be included in a final TUSS.
4. Prospective assessment of the TUSS in comparison with assessment by an experienced ultrasonographer.

3.2 Method

3.2.1 Study design

This study was an ultrasound study performed at the Churchill Hospital, Oxford which used an iterative process to develop and validate an ultrasound septation score.

In this chapter, 'degree of septation' means the overall subjective assessment by a thoracic ultrasonographer of the effusion as unseptated, mildly, moderately or heavily septated. As this was the only assessment of septation existing before the development of the TUSS, it has been used as the main comparator for this study.

3.2.1.1 Validation of subjective assessment of degree of septation with clinical outcomes

This phase of the study was a retrospective review of clinical outcomes associated with degree of septation of pleural effusions. The Oxford Pleural Service maintains a database of all thoracic ultrasounds and pleural procedures performed with a subjective assessment of degree of septation by an experienced thoracic ultrasonographer (trained to Royal College of Radiologist Level 1 standard or higher)

categorised as unseptated, mildly, moderately or heavily septated. This data was collected for the purpose of clinical information, not for this study and so interpretation of the results was necessary. This database was retrospectively reviewed to determine whether subjective assessment of a pleural effusion as being unseptated, mildly, moderately or heavily septated was associated with the following outcomes:

- For patients undergoing LAT:
    - 'Combined success' based on whether the procedure could be successfully performed and whether the biopsies correctly identified the presence of malignancy. Patients who were referred by other centres for LAT (i.e. those in whom long-term follow up data was not available) were not included in this data set. Biopsy results and final diagnosis were obtained from review of electronic patient records, radiology reports and clinic letters.
- For patients with pleural infection who underwent drain insertion:
    - Pleural infection associated 3 month mortality and need for surgery.
    - Length of hospital stay.
- For patients undergoing a therapeutic aspiration for relief of dyspnoea:
    - Decrease in VASD score (mm): This data was obtained as part of the study described in Chapter 2 of this thesis.

3.2.1.2 Development and testing a standardised protocol and determination of candidate factors

A list of potential factors which could be included in an US septation score was generated based on discussion with a specialist thoracic radiologist (Prof F Gleeson, University of Oxford) and chest physician (Dr N Rahman, Oxford Respiratory Trials Unit). These were:

- **Septation number**: The maximum number of septations crossed by a line drawn perpendicular to the probe at the maximally septated point.
- **Septation thickness**: The width of the thickest septation (mm).
- **Lung movement:** Presence of either visible movement of atelectatic lung within the pleural fluid or the sliding pleura sign seen above the level of pleural fluid (categorised as yes/no).
- **Fluid Doppler**: Presence of colour Doppler signal within the pleural fluid during breath hold (categorised as yes/no).
- **Homogeneity**: Homogeneity of effusion determined by whether no septations could be seen in the fluid; some ultrasound views included septations; or all ultrasound views included septations (categorised as unseptated/heterogeneously septated/homogenously septated).
- **Septation Doppler:** Presence of colour Doppler signal detectable within septations (categorised as yes/no).
- **Echogenic swiring:** The presence or absence of echogenic swirling within the pleural fluid (categorised as yes/no).

These factors were assessed in pilot work based on 20 US scans and from this work a standard protocol assessing 5 candidate factors for the TUSS was developed (Section 3.2.1.3.1).

3.2.1.3 Assessment of interrater reliability and association of candidate factors with degree of septation

In this phase of the study, 2 experienced thoracic ultrasonographers independently scored 50 pleural effusions using the candidate factors developed above. The ultrasonographers were respiratory physicians trained to Level 1 standard thoracic ultrasound as determined by the Royal College of Radiologists and were blinded to the results of the other physician. The ultrasounds were performed sequentially using the same ultrasound machine without moving the patient in between scans. Additionally, they assessed the degree of septation within the effusion as unseptated, mildly septated, moderately septated or heavily septated.

All adult patients (aged 18 years or above) with a pleural effusion requiring a thoracic ultrasound were eligible for inclusion in this study. Exclusion criteria were:

- Pleural thickening detected on US rather than pleural effusion;
- No evidence of pleural effusion on US;
- Unable to comply with the study protocol e.g. unable to sit in the correct position.

3.2.1.3.1 Ultrasound Protocol

Ultrasonographers followed the following protocol:

- Seat the patient on the edge of a bed with their arms resting on a table so the upper arms are horizontal, undressed so the entire thorax is accessible;
- Use 5-2 curvilinear probe with depth set to enable visualisation of the entire pleural effusion and chest/abdominal settings;
- Starting medially on the back, identify the costophrenic angle and then scan up towards the spine in that rib space assessing the effusion for number of septations and thickness of thickest septation;
- Repeat in the next rib space and move round laterally until the entire effusion has been assessed.
- Record the following factors:
    - **Septation number:** Greatest number of septations along a line draw perpendicular to the US probe;
    - **Septation thickness**: width of thickest septation (mm, to 1 decimal place);
    - **Lung movement:** Presence of either visible movement of atelectatic lung within the pleural fluid or the sliding pleura sign seen above the level of pleural fluid (categorised as yes/no).
    - **Fluid Doppler**: Presence of colour Doppler signal within the pleural fluid during breath hold (categorised as yes/no).
    - **Homogeneity:** Homogeneity of effusion determined by whether no septations could be seen in the fluid; some ultrasound views included septations; or all ultrasound views included septations (categorised as

unseptated/heterogeneously septated/homogenously septated);

3.2.1.3.2 Statistical analysis

Statistical analysis was performed using SPSS 20.0.0.

Interrater reliability of the blinded assessments of degree of septation by the ultrasonographers was assessed using the kappa statistic, with a kappa score of >0.75 preset to demonstrate that there is good agreement between observers.

Secondly, the interrater reliability of each candidate factor assessed was calculated. The kappa statistic was used for the categorical factors (lung movement, fluid Doppler and homogeneity) and intraclass correlation coefficient calculated for the continuous variables (number of septations and thickness of thickest septation). Bland-Altman plots were plotted of number of septations and thickness of thickest septation. Candidate factors which had a poor interrater reliability (preset as a Kappa score/correlation < 0.75) were not considered further for inclusion in the TUSS.

Next, chi-square test (for categorical factors) or ANOVA (for continuous factors) were used to assess which candidate factors were significantly associated with degree of septation. Candidate factors which had a poor association with degree of septation (preset as p>0.2) were not considered further for inclusion in the TUSS.

Stepwise linear regression was used to create a regression model to demonstrate which factors independently correlate and significantly

contribute to the degree of septation. These factors were included in the final TUSS.

3.2.1.4 Prospective validation

The final TUSS was prospectively validated compared with subjective assessment of degree of septation by experienced thoracic ultrasonographers, assessed using chi-square tests to confirm the outcome was associated with degree of septation. A further prospective validation is currently underway to see whether the TUSS can predict clinical outcomes. The same outcomes assessed in section 3.2.1.1 are being used to validate the score.

3.3 Results

3.3.1 Validation of subjective assessment of degree of septation with clinical outcomes

3.3.1.1 Local anaesthetic thoracoscopy

All LATs performed over 5 years (from December 2007 to November 2012) were reviewed. 239 LATs were attempted in local patients with a pleural effusion. There was a significant association between degree of septation and combined success rate of LAT (Table 3-1) (chi squared=28, $p<0.001$).

Table 3-1: Number and percentage of LATs successfully performed categorised by degree of septation

Degree of septation	Combined success of LAT (%)
Unseptated	154/161 (96%)
Mildly septated	32/36 (89%)
Moderately septated	11/18 (61%)
Heavily septated	18/24 (75%)

3.3.1.2 Patients with chest drain inserted for pleural infection

Data was available in 34 patients (Table 3-2). There was no significant difference in death and need for surgery or mean length of hospital stay between the groups.

Table 3-2: Death, requirement for surgery and mean length of hospital stay in patients with pleural infection categorised by degree of septation

Degree of septation	Number of patients dying or requiring surgery within 3 months (%)	Mean length of hospital stay (days) (range)
Unseptated	3/9 (33%)	25 (2-69)
Mildly septated	4/7 (57%)	18 (4-55)
Moderately septated	2/9 (22%)	12 (4-25)

Heavily septated	4/9 (44%)	16 (4-55)

3.3.1.3 Change in VASD

Paired data was available for baseline degree of septation and change in VASD following a pleural procedure in 81 patients. This data is summarised in Table 3-3.

Table 3-3: Mean decrease in VASD categorised by degree of septation

Degree of septation	**Number of patients**	**Mean decrease in VASD (mm) (SD)**
Unseptated	60	29 (20)
Mildly septated	14	36 (23)
Moderately septated	4	35 (15)
Heavily septated	3	-4.2 (50)

One-way ANOVA was conducted to assess the effect of degree of septation on decrease in VASD. This demonstrated a significant association between degree of septation and mean decrease in VASD ($F=2.8$, $p=0.043$). A Tukey post-hoc test demonstrated a significant difference between the mean decrease in VASD between the mildly and heavily septated groups but no other significant differences (Mean difference mildly septated-heavily septated 40mm, 95% CI 77 – 3.5mm).

3.3.2 Development and testing a standardised protocol and determination of candidate factors

In this phase, different protocols were trialled to identify:

1. A thoracic ultrasound protocol that would give consistent and valid results but be easy to teach and rapid to perform;
2. Factors to be measured in this protocol to use in the TUSS.

Initially, observations were performed in standard locations on the hemithorax e.g. mid-axillary line, 5th intercostal space. However, it was found that this type of protocol was susceptible to missing areas of septation and so an alternative protocol in which the ultrasonographer systematically scanned the entire hemithorax was developed.

At this stage, 2 factors were discarded from inclusion in further scanning protocols:

1. Presence of echogenic swirling: because this appeared to depend on the quality of the US machine used;
2. Whether a colour Doppler signal was detectable in septations: because this was not detectable.

The remaining factors were reassessed in the next phase.

An attempt was made at this phase to record US videos so that these could be scored by other ultrasonographers to assess interrater reliability. However, it was decided that the choice of views by the initial ultrasonographer to be used in the video meant that the second score was not independent of the first score and therefore, in the second phase of the study, interrater reliability was tested by 2

ultrasonographers scanning the hemithorax sequentially blinded to the results of the other.

3.3.3 Assessment of interrater reliability and association of candidate factors with degree of septation

In this phase of the study, 50 patients were scanned.

The interrater correlations for the degree of septation and the candidate factors assessed are summarised in Table 3-4.

Table 3-4: Interrater reliability of degree of septation and candidate factors

Candidate Factor	**Kappa score**
Degree of septation	0.85
Fluid Doppler	0.73
Lung movement	0.67
Homogeneity	0.80

Bland and Altman methodology was used to assess difference for septation number and septation thickness between the two raters. For septation number, mean difference was -0.31 (+/- 2.1, p=0.11) (Figure 3-2). For septation thickness, mean difference was 0.1 (+/- 3.9, p=0.73) (Figure 3-3).

Figure 3-2: Bland-Altman plot for septation number

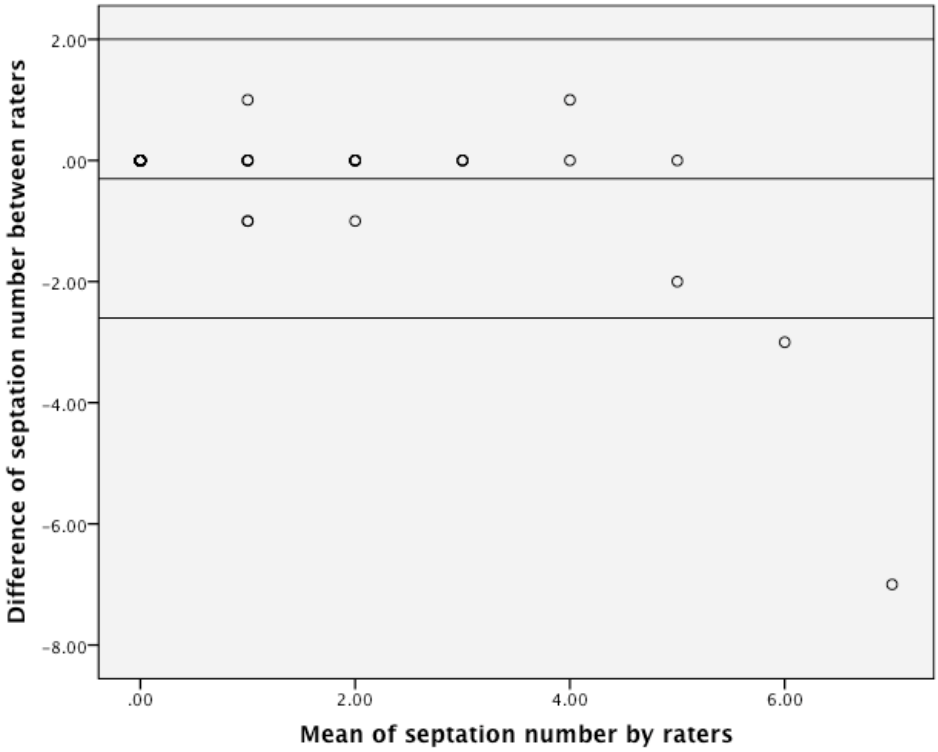
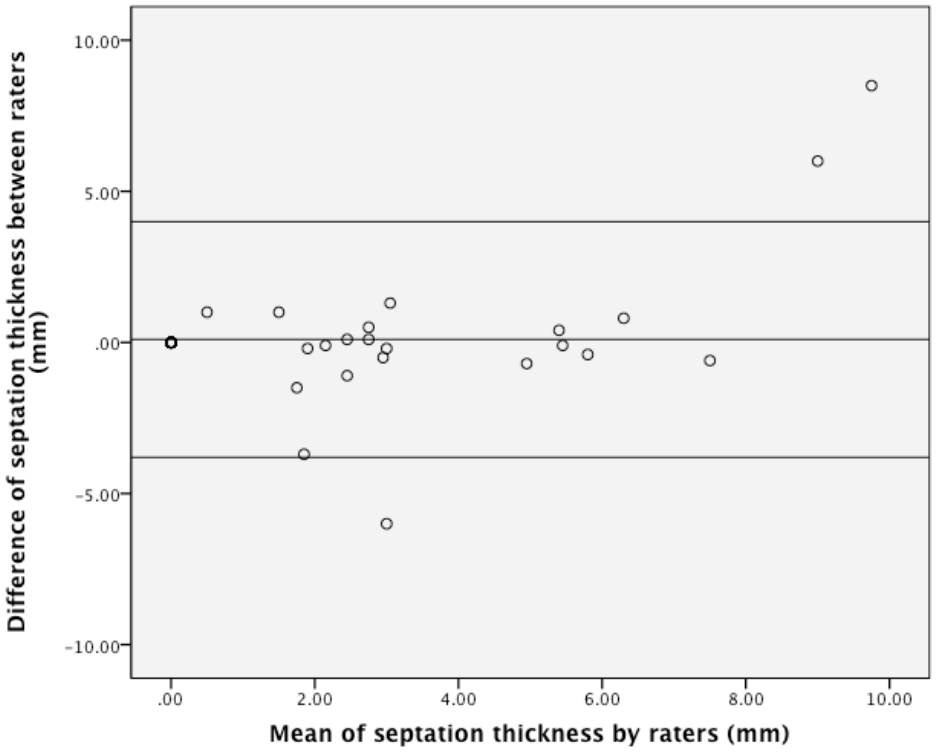


Figure 3-3: Bland-Altman plot for septation thickness



Data on septation number and septation thickness was not normally distributed due to a heavy skew because the majority of effusions assessed were unseptated. Therefore Kendall's tau was used to calculate correlation. Interrater correlation between septation number was 0.90 ($p<0.01$) and between septation thickness was 0.78 ($p<0.01$).

Due to the low interrater reliability of fluid Doppler and lung movement, these factors were not considered further for inclusion in the TUSS.

The remaining 3 candidate factors were then assessed for significant association with the degree of septation. All were significantly associated with the degree of septation(Table 3-5).

Table 3-5: Association of candidate factors with degree of septation

Candidate Factor	**Test of association**	**Result**
Septation number	ANOVA	$F(3,85)=150$, $p<0.001$
Septation thickness	ANOVA	$F(3,85)=41$, $p<0.001$
Homogeneity	Chi squared	$Chi=145$, $p<0.001$

Mean and range of values for septation number and septation thickness categorised by degree of septation are summarised in Table 3-6 and Table 3-7.

Table 3-6: Mean and range of values for septation number categorised by degree of septation

Degree of septation	**Mean septation number**

	(range)
Unseptated	0 (0-0)
Mildly septated	1.5 (1-3)
Moderately septated	3 (2-4)
Heavily septated	6 (3-10)

Table 3-7: Mean and range of values for septation thickness categorised by degree of septation

Degree of septation	**Mean septation thickness (mm) (range)**
Unseptated	0 (0-0)
Mildly septated	3.4 (1.0-6.0)
Moderately septated	5.0 (1.0-14)
Heavily septated	4.3 (1.0-7.8)

Stepwise linear regression demonstrated that all 3 candidate factors independently predicted degree of septation (Adjusted R square=0.93, $F(3,85)=380$, $p<0.001$).

Table 3-8: Results of stepwise linear regression analysis

Candidate factor	**Standardised coefficients (beta)**
Homogeneity	0.94 ($p<0.001$)
Septation number	0.39 ($p<0.001$)
Septation thickness	0.13 ($p<0.001$)

Despite the fact that septation thickness did contribute to prediction of the degree of septation of an effusion, a decision was made

not to include it in the final score because the mean septation thickness was less for heavily septated effusions than for moderately septated effusions.

The final TUSS was determined to be an assessment of:

1. **Septation number:** Greatest number of septations along a line drawn perpendicular to the US probe divided into 4 categories (0, 1-2, 3-4, >=5). The values for these categories were chosen based on the mean and range of septation number in the data previously collected (Table 3-6).
2. **Homogeneity:** Homogeneity of effusion determined by whether no septations could be seen in the fluid (unseptated); some ultrasound views included septations (heterogeneously septated); or all ultrasound views included septations (homogenously septated).

The data collected on degree of septation categorised by homogeneity and septation number is summarised in Table 3-9

Table 3-9: Mean and range for septation number categorised by degree of septation and homogeneity

Homogeneity	**Degree**			
	Unseptated	**Mild**	**Moderate**	**Heavy**
Unseptated	0 (0-0)	-	-	-
Heterogenously septated	-	1 (1-3)	3 (2-4)	-
Homogenously	-	-	3.5 (3-4)	5 (3-10)

septated				

Table 3-9 demonstrated that there is not a simple scoring system that can be used to convert the septation number and homogeneity into the degree of septation. For this reason, and to keep the scoring system simple, it was decided that prospective data should be gathered on septation number and homogeneity, rather than attempting to combine both factors into a single score.

3.3.4 Prospective validation

15 patients were scanned to prospectively validate the final TUSS. The same protocol was used as determined previously but only degree of septation, homogeneity and septation number (categorised as 0, 1-2, 3-4 and >=5) were assessed. Homogeneity and septation number were confirmed to be highly associated with degree of septation (septation number chi-square=33, $p<0.001$, homogeneity chi square=45, $p<0.001$).

3.4 Discussion

This study describes the iterative process used to develop and validate a TUSS which has the potential to be used to predict outcomes and guide patient management.

3.4.1 Validation of subjective assessment of degree of septation with clinical outcomes

The first step was to demonstrate that subjective assessment of the degree of septation by an experienced thoracic ultrasonographer predicted important clinical outcomes. My results demonstrate that

degree of septation on baseline ultrasound predicts combined success of LAT (i.e. whether the procedure will be successfully performed and whether malignancy will be correctly diagnosed) and decrease in VASD following a pleural procedure. The mean decrease in VASD in patients with a heavily septated effusion was less than the MID, suggesting that alternative treatments should be used in this patient group. However, there was wide variation in response and only small numbers of patients with heavily septated effusions. In contrast, in patients treated with a chest drain for pleural infection, there did not appear to be a relationship between need for surgery or death within 3 months or length of stay and degree of septation, although numbers of patients were small. Predicting whether these procedures will be successful early allows planning of an alternative management plan, e.g. use of cutting needle biopsies rather than LAT in the case of undiagnosed pleural effusion, or alternative treatment strategies to palliate breathlessness in the case of pleural procedures.

It is possible that a greater association with these clinical factors will be found with an objective TUSS rather than the subjective assessment made and for this reason a potential relationship between degree of septation and clinical outcome in patients with pleural infection should not be dismissed at this point.

This data collection was limited by the small number of septated effusions. The data was not collected for this purpose, patients were not scanned in a standarised manner and the data was reviewed retrospectively, which limits the reliability of the data obtained.

3.4.2 Development and testing a standardised protocol and determination of candidate factors

Developing a standardised protocol for the assessment of septation was difficult due to the large variation in anatomy of pleural effusions and their heterogenous nature, particularly of septated effusions. Attempts to make measurements at standardised locations on the patient failed to accurately assess degree of septation because areas of septation were missed. Therefore an approach had to be chosen that involved methodically scanning the entire effusion and choosing the most septated area. It could be argued that choice of the most septated area will be a subjective assessment by the ultrasonographer, but ultrasound is necessarily an operator-dependent assessment.

3.4.3 Assessment of interrater reliability and association of candidate factors with degree of septation

Interrater reliability for degree of septation, homogeneity, septation number and septation thickness were excellent. Values of kappa greater than 0.75 are often taken to represent excellent agreement. The kappa score for assessment of degree of septation between the 2 ultrasonographers was 0.85. The correlations between septation number and septation thickness were also extremely high, suggesting that these factors can all be reliably assessed.

Homogeneity and septation number were very strongly associated with degree of septation and were able to predict most of the variability

of degree of septation. Therefore these 2 factors are excellent choices for a final septation score.

3.4.4 Prospective validation

A limitation of the current prospective validation is that the ultrasonographers were aware of the assessment underway and this may have influenced their assessment of the degree of septation of the effusion. Further prospective validation with objective clinical outcomes is essential for the validation of this TUSS and is currently underway.

3.4.5 Limitations

Ultrasound is a subjective skill and the assessment of an experienced operator is the gold standard for septations. If a scoring system is going to aid the management of patients, thoracic physicians with less ultrasound experience need to be able to score patients. Transforming a subjective assessment into a simple objective scoring system is a major challenge.

A major problem limiting data collection in this study was the small proportion of septated pleural effusions compared to unseptated effusions, which meant a large number of scans had to be performed in order to collect enough data. This was a particular problem when attempting to validate the score with other measures of the effectiveness of pleural fluid drainage.

3.4.6 Future directions

The TUSS will be used to prospectively assess all pleural effusions scanned by the Oxford Pleural Service over 6 months. Data will be collected on the following factors:

- For patients undergoing LAT:
    - Whether the procedure was successfully performed;
    - The sensitivity and specificity of the procedure.
- For patients with pleural infection who underwent drain insertion:
    - Pleural infection associated 30 day mortality and need for surgery.
- For patients undergoing therapeutic aspiration:
    - The decrease in dyspnoea measured with the VASD.

This data will then be analysed to demonstrate the external validity of the TUSS.

3.5 Conclusion

This study demonstrates the validation and development of a TUSS. Further prospective validation is underway. The TUSS has the potential to be a useful clinical and research tool.

4 Effect of an indwelling pleural catheter versus standard care for relieving dyspnoea in patients with malignant pleural effusion: the TIME2 randomised controlled trial

4.1 Introduction

This chapter reports the TIME2 randomised controlled trial, an RCT comparing indwelling pleural catheters (IPCs) with standard care of patients with breathlessness secondary to a malignant pleural effusion (MPE). Standard care of patients presenting with a new MPE is chest drain and talc pleurodesis[1]. However, indwelling pleural catheters (IPCs) have become an increasingly popular alternative to this. Since the approval of IPCs by the Food and Drug Administration in the United States in 1997, use has risen to over 39,000 per year[145]. Despite this increase in use, the comparative efficacy of standard care and IPCs at relieving dyspnoea and improving quality of life had not been fully assessed prior to this trial.

4.1.1 Standard care

Standard first line care of patients with MPE as recommended by the current British Thoracic Society guidelines is admission to hospital, insertion of a chest drain, drainage to dryness followed by talc slurry pleurodesis[1]. Advantages of this treatment modality are that it is

simple and readily available. However, acute complications of talc pleurodesis include significant chest pain in 7%, fever and hypoxia[1, 97, 99, 146, 147]. Median hospitalisation in a previous study was 7 days, on average 7.5% of these patients' remaining lives[148]. It is ineffective in patients with trapped lung i.e. those in whom the lung fails to re-expand to come into contact with the chest wall following drainage of pleural fluid, and septated effusion, both conditions which may not be recognised until treatment has been started. The 30 day pleurodesis failure rate, defined as need for a further pleural procedure due to dyspnoea, is approximately 30%[93]. Following failed pleurodesis, further management is more difficult due to loculation of fluid. Often these patients will repeatedly attend hospital for recurrent aspiration.

4.1.2 Indwelling pleural catheters

Indwelling pleural catheters (IPCs) are semi-permanent drains which are tunnelled under the skin and then inserted into the pleural space using a guide-wire technique. They can be inserted as a day case procedure under local anaesthetic without sedation, followed by large volume pleural fluid drainage. The patient, carer or district nurse is then trained in drainage of the IPC. Drainage is performed by removing the valve cap from the IPC, connecting the drainage bottle which is vacuum sealed and then pressing the button of the drainage line to release the vacuum. Sterile technique is essential to reduce the risk of IPC infection. Drainage can be performed on a regular basis or only if the patient is breathless. IPCs offer the advantages of outpatient management of MPEs and patient control over symptoms [149, 150]. Disadvantages include frequent complications, the nuisance of a long-term catheter

requiring dressing and the need for on-going drainage. Rather than being a definitive treatment, approximately 10% of patients will require a further procedure.

4.1.2.1 Complications

Complications of IPCs can be classified into early complications, due to drain insertion, and late complications, due to prolonged presence of a foreign body in the pleural space and subcutaneous tissues. Early complications include subcutaneous emphysema, pleural infection, bleeding, pain and failure of insertion[151]. Late complications include empyema, displacement, catheter tract metastases and blockage[152, 153]. The complications of IPCs seen in previously published case series and trials are summarised in Table 4-1. Complications are common, with a recent systematic review reporting an overall complication rate of 13%. Complications may have been underreported in the studies reviewed by this systematic review as there is no consensus of what complications should be reported and a large proportion of the studies reviewed were retrospective case series[150].

Pleural infection is the most serious common complication, often requiring hospital admission for intravenous infections, although it only rarely is considered to contribute to death. Concurrent chemotherapy is not a risk factor for developing a pleural infection[154].

4.1.2.2 Spontaneous pleurodesis (SP) and catheter removal

SP in patients with an IPC is the spontaneous ablation of the pleural space so no further fluid accumulates and no further drainage

occurs. This may occur due to the presence of a foreign body in the pleural space causing low-grade inflammation combined with apposition of the pleural membranes due to regular drainage of the pleural fluid. Clinicians need to distinguish this from IPC blockage associated with a residual pleural effusion using chest radiograph or ultrasound, which should be treated with saline flushes or fibrinolytics so that the patient can resume regular drainage and prevent recurrence of dyspnoea. Once SP has occurred, the IPC can be removed, in order to decrease the risk of pleural infection and cellulitis and remove the nuisance to the patient of the drain. Removal is performed under local anaesthetic as a day case procedure and requires dissection of the cuff from the subcutaneous tissues which anchor it. The remainder of the IPC can usually be easily removed by pulling on it, but in approximately 9.8% of cases IPC removal is complicated by catheter fracture during the removal attempt or failure of complete removal due to growth of malignant cells into the holes in the IPC[155]. However, failure of complete removal does not appear to result in complications and so surgical removal is not required in these cases.

Average length of stay of the IPC ranges from 29-87 days in published literature[149, 151, 153, 156-158]. This variation is in part due to difference in criteria for removal. Spontaneous pleurodesis rate in published series varies from 21-76%[148, 149, 151, 156-158]. Again, this variation is due to a lack of consensus definition of SP, with some researchers defining it as IPC removal, regardless of whether further pleural procedures are required. Tremblay et al. found that if IPCs were removed once patients had drained less than 50ml of pleural fluid on

three consecutive drainage attempts (patients having been advised to drain three times weekly) without progressive symptoms or reaccumulation of fluid on CXR, 13% required further ipsilateral pleural procedures[153]. Further pleural procedures, particularly repeat IPC placement, may be more difficult following IPC removal. For these reasons, our department has adopted a more conservative approach to IPC removal. Our standard practice is to remove IPCs once there has been no drainage for 6 weeks and there is no radiographic evidence of significant fluid recurrence, and this was the practice recommended to other recruiting centres.

4.2 Literature review

4.2.1 Previous randomised trials

Controversy exists as to whether IPCs or standard care are more effective at palliating symptoms and improving quality of life in a cost effective manner[159]. Two previous RCTs have compared standard treatment with IPCs for the first line treatment of MPEs. Putnam et al. [160] randomised 144 patients in a 2:1 ratio to IPC or chest drain and doxycycline pleurodesis respectively. All patients were admitted for IPC insertion, whereas common practice is now outpatient insertion. Median initial hospitalisation of patients receiving an IPC was 1.0 day compared to 6.5 days in the standard treatment group (p<0.001). Three different measurements of dyspnoea were used at a 30 day interval to compare the groups: Borg category ratio 10 (CR10) scale at rest, Borg CR10 Scale during exercise and chronic respiratory disease questionnaire dyspnoea subsection. The Borg CR10 scale is a 0-10 rating scale for

different levels of dyspnoea, with descriptions such as 'very slight' and 'moderate' anchored to different points of the scale[161]. None of these measure showed a significant difference in dyspnoea at any time point but there was high loss to follow up. Pain was assessed 24 hours after drain insertion and no significant difference was found between the groups. Quality of life was not assessed.

The second RCT only recruited 57 patients out of a required 530 over 2 years[162]. The primary outcome was a 'successful' treatment at 30 days, defined as:

(1) Alive with no effusion recurrence;
(2) Lung re-expansion >=90% after effusion drainage; and
(3) Completion of the intervention by 2 weeks defined as removal of the chest drain for standard care or proper function of the IPC.

No significant difference was found in this outcome. Patients treated with IPC had significantly better 30-day activity without dyspnoea scores. The poor recruitment was due to randomisation refusal, with patients preferring to chose one or the other treatment.

The limitations in these two trials mean there was a need for a further randomised trial comparing IPCs with standard care powered for the important outcome of relief of dyspnoea.

4.2.2 Published case series

Although several case series of patients who have had IPCs inserted have been published, in general the quality of published

evidence is poor, with most data being retrospectively collected and with short follow up[151, 156, 157]. These case series are summarised in Table 4-1. One recent prospective case series compared patients who were treated with IPC with those treated with standard care, and found that patients who were treated with an IPC had fewer hospital bed days, required fewer pleural procedures and had no difference in rates of pleural infection[163]. Choice of treatment was made by the patient and their physician. These patients were not randomised to the two treatments and baseline performance status was not reported, so it is possible that these results are due to bias in treatment selection by the physician and patient.

Table 4-1: Summary of previously published case series of patients with IPCs

Study	Outcomes	Complications	Follow up
Al-Halfawy 2008 [164] Case series 55 IPCs All patients	SP 42 (76.3%). Mean period of drainage 19.1 days (range 12-59 days).	1 pleurodesis failure requiring aspiration, no device-related complications (no comment on other complications). NB Aim was to assess alternative system of drainage	3 months following catheter removal

Study	Outcomes	Complications	Follow up
Bazerbashi 2009[151] Retrospective case series 125 IPCs Only patients with trapped lung, failed previous pleurodesis	Median stay 87 days (5-434). 77.6% patients discharged home within 2 days. Pleurodesis in 76% (no drainage on 2 occasions, CXR showing no fluid collection)	15 (12%). Early: 7 subcutaneous emphysema, 3 empyema, 3 pneumothorax, 3 catheter displacement, 1 conversion to mini-thoracotomy. 6 weeks post op: 7 wound infection, 3 recurrent effusion, 2 catheter leak, 2 catheter blockage requiring removal, 1 tumour dissemination, mild to moderate pain at catheter site in 11 patients.	Not specified. Data collected at arbitary time point, so many patients still alive with IPCs in.
Bertolaccini 2007[165] Case series 48 IPCs Patients with recurrent malignant pleural effusions	Mean stay 88 days. Drained average of 7 days. SP in 23/48 (47.9%) patients, mean time 43 days	No major complications.	Not specified

Study	Outcomes	Complications	Follow up
Bertolaccini 2012[166] Case series. 90 patients. Patients with recurrent MPE	Mean time to pleurodesis 51 days. SP in 37 (41.1%) patients.	No major complications	Not specified
Efthymiou 2009[167] Retrospective case series 116 IPCs inserted, only 48 responded. Trapped lung	50% of patients moderately satisfied with improvement in mobility,	Pain 35%, lasted <3 days. But complications were patient reported, not from notes review. 4% occlusion and catheter displacement requiring IPC replacement, 13% peri-catheter leakage	Not specified
Fysh 2012[163] Prospective case series. 34 IPCs. Symptomatic MPEs	Total hospital day 6.5 days, representing 8% of remaining life.	Symptomatic loculation/failed pleurodesis 5 (13.5%), empyema 4 (10.8%), haemothorax 1 (2.7%), dislodgement of catheter 1 (2.7%)	Minimum of 3 months

Study	Outcomes	Complications	Follow up
Mullett 2003[168] Retrospective case series. 79 IPCs. All patients.	11/69 (16%) required subsequent procedures typically drain replacement. Drain removal in 36/69 (52%)	1 failed insertion	Not specified
Murthy 2006[156] Case series. 63 IPCs. Patients with poor PS or failed other therapies	No further intervention in 95%. 50/58 (86%) experienced dyspnoea relief.	1 pneumothorax, 1 seroma, 1 empyema, 1 pain syndrome. 4/63 (6%) required tPA	Specific date (minimum of 4 days)

Study	Outcomes	Complications	Follow up
Musani 2004[169] Retrospectve case series. 24 IPCs. Patients with recurrent symptomatic MPEs	Symptomatic relief in 100% of patients, SP in 58% of patients in mean 39 days.	Localised celluitis 3/24, empyema 3/24, 1 catheter tract metastases. 1 failure requiring repeat IPC placement	Not specified
Ohm 2003[170] Case series. 34 IPCs Patients with trapped lung	Length of stay 2.8 days in outpatients, 9.4 days in inpatients	None reported (conference abstract)	Not specified
Pien 2001[171] Retrospective case series 13 IPCs. Patients with trapped lung	10/11 symptomatic benefit (improved dyspnoea and exercise tolerance)	2 ?empyema/?catheter colonisation, localized skin breakdown, possible cellulitis, 1 catheter occlusion requiring replacement	Not specified

Study	Outcomes	Complications	Follow up
Pollak 2001[172] Case series 31 IPCs Group of patients not specified	Dyspnoea improved in 94% (29 of 31). Control of MPE in 28/31. SP in 13/31 (42%)	Early transient catheter-related pain common.	Not specified
Putnam 2000[148] Retrospective case series 100 IPCs All patients.	Early costs are less in outpatient IPC patients compared with inpatient IPC patients or usual care	19% had complications: 8 patients developed fluid recurrence requiring therapy (symptomatic loculation); 8 patients had removal of a malfunctioning catheter; 5 patients developed empyema requiring additional treatment.	Until death/IPC removal
Robinson 1994[173] Case series 12 Tenckoff catheters All patients	Mean drainage	3 cellulitis	Death

Study	Outcomes	Complications	Follow up
Schneider 2009[157] Case series 100 IPCs All patients	SP in 29%. Median residence time 70 days	4 empyemas, 2 accidental dislodgement, 3 malfunction of drainage	Not specified
Storis 2009[174] Retrospective case series 51 IPCs Patients unsuitable for talc	Discharge home on following day in 71%	15% developed infection, air leak or blockage. SP in 21%	2 years later
Suzuki 2011[145] Case series 418 IPCs All patients	'Palliation' – no other drainage procedures in 380/418. 91% success, 26% SP	20/418 (4.8%). 17 patients had second ipsilateral IPCs. 4 cellulitis, 6 empyema all of which required catheter removal, replacement with chest tubes in four and open drainage in 2. Ipsilateral pneumothorax. 7 blockages, 2 dislodgements. 37 cases IPC removed, effusion recurred.	Median follow-up 2.4 months

Study	Outcomes	Complications	Follow up
Tremblay 2006[158] Prospective case series 250 IPCs All patients	SP 42.9%, no further ipsilateral pleural procedures in 90%	10 failed insertions (4%), symptomatic loculation 8.4%, empyema 3.2%, pneumothorax/surgical emphysema/bronchopleural fistula 2.4%, cellulitis 1.6%, recurrent fluid 1.6%, dislodged 1.2%, bleeding 0.8%, tumour seeding 0.4%, pain requiring removal 0.4%, extrapleural catheter 0.4%	Until IPC removal or death
van den Toorn 2005[175] Retrospective case series 17 IPCs Patients with MPEs		Infection 12%, dislocation of catheter 18%, 'catheter use was unstatisfactory' 12%	Not specified

Study	Outcomes	Complications	Follow up
Warren 2008[149] Retrospective case series 295 IPCs Patients with MPEs	SP in 59%	Catheter blockage (3.7%), cellulitis 1.3%, empyema 0.3%, catheter tract metastases 0.3%	Review in July 2006

4.2.3 Cost

Treatment cost is an important factor in deciding whether standard treatment or IPCs should be used in the first line therapy of patients with MPEs. Initial treatment costs of IPCs are lower, because they can be inserted as an out-patient while chest drain and pleurodesis requires a significant inpatient stay[148]. However, on-going costs of IPCs include the cost of drainage bottles, nursing support and treating complications, which may involve an inpatient stay. A cost-effectiveness analysis based on previously published data suggests similar cost effectiveness for the 2 interventions, with standard care being less costly than an IPC for patients surviving more than 6 weeks but IPC being less costly for patients surviving less than 6 weeks[176]. A full economic assessment is required to test which treatment approach is more cost effective, and this is being performed as part of this study but will not be reported in this thesis.

4.2.4 Trial Design

4.2.4.1 Primary objective and hypothesis

The primary objective of this study was to determine whether patients treated with IPCs experience less daily dyspnoea over 42 days than patients treated with standard care. We hypothesised that in the situation that patients became breathless due to recurrence of pleural fluid, patients with IPCs would be able to relieve their breathlessness straight away by draining their own fluid, whereas standard care patients would have to wait while they organised a hospital attendance and underwent a painful procedure. Therefore patients with an IPC would experience less breathlessness overall.

The primary outcome measure in this study is daily dyspnoea intensity measured by a visual analogue scale (VAS). This is a 100mm line anchored at one end by 'not breathless at all' (0mm) and the other by 'worst possible breathlessness' (100mm). Subjects are asked 'On average, how breathless have you felt over the last 24 hours?' They draw a mark perpendicular to the line based on their assessment of their dyspnoea. The distance to this mark from 0mm is measured to calculate the VAS score. The VAS was chosen because it has been shown to be a valid, reliable and reproducible measurement of dyspnoea[124, 177]. It allows rapid daily assessment of dyspnoea so it is sensitive to change. Although the daily mean VASD has not been used in this way in previous studies, VAS scores have used to quantify daily chronic pain in pain trials[178]. A daily assessment of dyspnoea for 42 days was chosen rather than a single measurement at 42 days because patients' levels of dyspnoea will fluctuate significantly based on the volume of pleural fluid

in their chest. A period of 42 days was chosen because it represents a significant proportion of the remainder of these patient's life without being too much of a burden for the patients to comply with.

4.2.4.2 Secondary objectives and hypothesis

Important secondary objectives were:

1. To determine whether patients treated with IPCs or those treated with standard care experienced less chest pain: We hypothesised that the standard care patients would experience more chest pain because they had to undergo a painful pleurodesis procedure. This was assessed using a daily visual analogue scale (VAS) for which patients were asked 'On average, how much chest pain have you experienced over the last 24 hours?'
2. To determine whether patients treated with IPCs or those treated with standard care experienced a better quality of life: We hypothesised that patients with an IPC would spend more time at home, be less breathless and be in control of their own disease and therefore experience a better overall quality of life.

Other factors assessed included length of hospitalisation, fever in the first 7 days, adverse events, number of patients crossing over between the groups and spontaneous pleurodesis rate in the IPC group. Patients were also asked about the unpleasantness of their dyspnoea and chest pain, because these subjective symptoms are recognised to cause unpleasantness which varies independently from intensity[179, 180]. Fever was assessed because talc is known to cause systemic inflammation and fever and it was hypothesised that the IPC patients

would not experience this inflammatory reaction and hence have lower rates of fever[97].

The Chronic Respiratory Disease Questionnaire (CRDQ) was also used, looking specifically at the total CRDQ score and dyspnoea and mastery domains. The CRDQ is a respiratory disease specific questionnaire, validated in different groups of respiratory patients, particularly in those with chronic obstructive pulmonary disease, but has not been validated in MPEs. It consists of 4 different domains (dyspnoea, emotional, fatigue and mastery). As well as the total score and dyspnoea domain, the mastery domain was chosen as an outcome because it was hypothesised that patients with an IPC in situ would have more control over fluid drainage and hence score more highly on the mastery domain.

4.3 Methods

4.3.1 Study design

This was an open-label randomised controlled trial (The Second Therapeutic Intervention in Malignant Effusion Trial (TIME2)) which recruited patients with symptomatic recurrent malignant pleural effusion from April 2007 to February 2011. Patients were allocated to standard care (chest drain and talc pleurodesis) or indwelling pleural catheter (Rocket Medical, Washington, UK) in a 1:1 ratio.

4.3.2 Trial management systems

The trial was sponsored by the University of Oxford. The trial was coordinated from the UK Clinical Research Network Oxford Respiratory

Trials Unit (UKCRN ORTU) with Oxford University Hospitals NHS Trust acting as the main recruiting centre. Trial management was by the UKCRN ORTU.

4.3.3 Funding

The trial was funded by the British Lung Foundation and Rocket Medical provided the catheters and drainage bottles free of charge. None of these bodies had any involvement in conduct, data collection, analysis or publication of the trial result.

4.3.4 Randomisation procedure

Randomisation occurred through a telephone system based at the Medical Research Council Clinical Trials Unit (MRC CTU) during weekday working hours. Given the semi-elective nature of the procedures, no system was required for 'out of hours' randomisations.

Eligible patients were given the Patient Information Sheet and at least 24 hours to consider whether they wanted to be enrolled into the study. They then completed a consent form. The investigator then completed a randomisation case report form (CRF) which included information on patient identification (initials, date of birth, country of birth and randomising centre). The investigator telephoned MRC CTU which checked all the inclusion and exclusion criteria and collected the identification and minimisation information. At randomisation, each patient was assigned a three digit trial number (e.g. 001) and the randomising clinician was informed of the treatment group the patient had been allocated to.

Patients were allocated in a 1:1 ratio to either IPC or standard care using minimisation with a random component of 80%. Minimisation criteria were histological tissue type (mesothelioma versus non-mesothelioma) and World Health Organisation (WHO) performance status (0/1 versus 2/3)[181]. These criteria were chosen because tumour type influences pleurodesis success, with mesothelioma having a higher rate of pleurodesis failure and performance status will influence length of hospital stay, mortality and dyspnoea[182].

4.3.5 Recruiting Centres

Initially, the study planned to recruit at Oxford University Hospitals NHS Trust only, but due to slow recruitment 5 further centres were opened. The recruiting centres and Principal Investigators (PIs) were:

1. Oxford University Hospitals NHS Trust: PI Dr Najib Rahman
2. Buckinghamshire Healthcare NHS Trust: PI Dr Anjani Prasad
3. Great Western Hospital, Swindon: PI Dr Andrew Stanton
4. James Cook University Hospital, South Tees: PI Dr Anur Guhan
5. Royal Berkshire Hospital, Reading: PI Dr Christopher Davies
6. University Hospital of North Tees: PI Dr Richard Harrison

No trial specific funding was provided to the centres or any trial specific research staff, but the study was approved by the UK Clinical Research Network (UK CRN) which meant that national funding was given to the centres based on recruitment to this (and other) trials which paid the salary of the local UK CRN research nurse. The PI in each centre was a respiratory physician who was delegated local trial

responsibility by ORTU. Local PIs delegated responsibility for randomisation and trial delivery to local staff. All researchers underwent Good Clinical Practice training.

Each centre was visited once local ethical approval had been given to inform them of trial delivery and management processes. They were supported by the ORTU and were able to contact the Trial Clinical Fellow via mobile phone at any time for reporting adverse events or advice. Newsletters were published to encourage recruitment and inform the local trial teams of any important changes to the trial.

4.3.6 Subject characteristics

4.3.6.1 Inclusion criteria

Patients with a clinically confident diagnosis of malignant pleural effusion requiring pleurodesis were eligible. The diagnosis was established by either:

- Histocytological proof of pleural malignancy; or
- The presence of a recurrent large pleural effusion in the context of histologically proven cancer outside the pleural space.

This meant that all patients enrolled had had a previous ipsilateral pleural aspiration, either diagnostic or therapeutic.

Histocytological proof was not required in all cases because a pleural effusion in a patient with known cancer is most likely to be due to metastatic disease and obtaining histocytological proof would delay treatment and decrease recruitment.

4.3.6.2 Exclusion criteria

These were:

- Age < 18 years,
- Expected survival < 3 months,
- Chylothorax,
- Previous lobectomy or pneumonectomy on the side of the effusion,
- Previous attempted pleurodesis,
- Pleural infection,
- Total blood white cell count < $1.0x10^9$,
- Hypercapnic ventilatory failure,
- Pregnancy,
- Lactating mothers,
- Irreversible bleeding diathesis,
- Irreversible visual impairment,
- Inability to give informed consent or comply with the protocol.

4.3.6.2.1 Rationale for these exclusion criteria

Patients with an expected survival < 3 months were excluded in order to improve data quality, because the primary outcome was measured over the first 42 days. This exclusion criteria was subjective and at the discretion of the randomising physician.

Patients with chylothorax, previous lobectomy or pneumonectomy of the side of the effusion and pleural infection were excluded because these patients would not normally be treated with chest drain and talc pleurodesis.

This study was of first line treatment for MPEs, so patients who had previously been treated by pleurodesis were excluded. IPCs are already a standard treatment for patients who have failed pleurodesis[1].

Patients who are neutropaenic (i.e. total blood white cell count < $1.0x10^9$) would be at greater risk of pleural infection with a long term foreign body, so would not be eligible for an IPC and were also excluded.

Patients with hypercapnic respiratory failure were excluded because of the potential for talc to worsen their respiratory function.

Patients with an irreversible bleeding diathesis were excluded as it would not be safe to insert a chest drain.

Patients with irreversible visual impairment were excluded because they would not be able to complete the VAS diary, which was the primary outcome.

Screening logs of all participants fulfilling the inclusion/exclusion criteria were kept, documenting reasons for non-inclusion.

4.3.7 Trial interventions

4.3.7.1 Indwelling pleural catheters

IPCs (Rocket Medical, Washington, UK) were inserted using a standard technique as a day-case procedure unless the patient was already an inpatient[169]. Patients gave written informed consent for the risks of bleeding, infection and pain. IPCs were inserted with the patient in the lateral decubitus position and an US was performed prior

to drain insertion to determine a safe location for insertion. Sterile technique was used including sterile gown. Sedation and antibiotic prophylaxis was given at the discretion of the performing clinician, but the majority of patients did not receive prophylactic antibiotics. Local anaesthetic was used to anaesthetise the pleura and a tract underneath the skin. The drain was then tunnelled under the skin and inserted into the pleural space using a guidewire technique. One closing suture was used to close the insertion site and a further securing suture was used to hold the IPC in place until the cuff was secured in the subcutaneous tissues. The IPC was then attached to a standard chest drain bottle with an underwater seal and the patient underwent an initial large volume drainage as tolerated. All patients had a CXR on the day of IPC insertion to confirm the IPC was correctly sited. They (or relatives or community nurse) underwent training in IPC management, either on the day of IPC insertion or at a hospital visit 1-3 days later. The training session lasted approximately 2 hours and included drainage of the effusion. The training was repeated as many times as required until the person draining the IPC was competent to drain it independently. The closing suture was removed either at hospital or at the patient's GP surgery after approximately 7 days. The holding suture was removed by the research team after at least 2 weeks following assessment to ensure the cuff was secure in the subcutaneous tissues. Patients were advised to initially drain three times weekly or as required for relief of dyspnoea. As drainage volume decreased, they were advised to decrease the frequency of drainage. Patients were advised to contact the research team if they had any concerns about the IPC, particularly increased

pain, change in pleural fluid appearance, redness around the insertion site and failure of drainage.

The IPC was removed once significant drainage ceased for at least 6 weeks with no evidence of significant fluid recurrence on either CXR or US. Other indications for drain removal were if the patient requested it or if there was no symptomatic relief from pleural drainage.

Patients who had an IPC inserted and an underlying diagnosis of mesothelioma had prophylactic radiotherapy to the drain insertion site to decrease the risk of catheter tract metastases.

4.3.7.2 Standard care

Patients randomised to standard care were admitted to hospital and managed according to British Thoracic Society treatment guidelines for chest drain insertion and talc pleurodesis[1]. Patients gave written informed consent for the risks of bleeding, infection and pain. Chest drains were inserted with the patient sitting up with arms resting on a table in front of them. US was performed prior to drain insertion to determine a safe site within the safe triangle. Sterile technique was used including sterile gown. Sedation and antibiotic prophylaxis was not given. Local anaesthetic was infiltrated into the skin and pleura. Chest drains inserted were 12F guide wire (Rocket Medical, Washington, UK) and were connected to a standard chest drain bottle with underwater seal. Drains were secured with 1 holding suture and dressed to prevent accidental dislocation. CXR was performed to confirm the chest drain was correctly situated. Large volume drainage of pleural fluid was done, with a maximum of 1.5l in the first hour and 1.5l every 2 hours

subsequently. Drains were flushed four times daily with 20ml normal saline. All patients were given heparin thrombosis prophylaxis (dalteparin 5000u subcutaneously once daily) unless there was a contraindication. Once drainage volumes had dropped, a repeat CXR was performed. Once complete drainage was confirmed radiologically, talc pleurodesis was conducted according to a standard operative procedure using 4g sterile high grade talc (Novatech UK) (Appendix B: Standard Operating Procedure for Talc Slurry Pleurodesis). Patients were given 5-10mg oramorph as premedication followed by intrapleural lidocaine 7mg/kg up to a maximum dose of 250mg. Sterile talc was suspended in 40ml normal saline and injected into the pleural space via the chest drain and the chest drain was then flushed with normal saline and the drain clamped for 1 hour. Patient rotation was not performed. The drain was then either left on free drainage or connected to thoracic suction (low pressure, high volume, from -5cm water to -20cm water as tolerated by the patient), as decided by the PI. Once drainage had dropped to <150ml/24 hours (excluding the volume from drain flushes), the chest drain was removed and the patient could be discharged. The chest drain was removed after 5 days regardless of drainage volume. Subjects with extensive 'trapped lung' on CXR (failure of >50% of lung surface to reach chest wall as assessed by the local PI) did not undergo pleurodesis but the chest drain was removed and they remained in trial follow up. If the drain was accidentally dislodged, it was only replaced if clinically indicated for continued pleural fluid drainage.

Patients in the standard treatment arm who developed symptomatic pleural fluid reaccumulation were managed with

therapeutic aspiration or IPC insertion, but investigators attempted to manage them using therapeutic aspiration only in the first 6 weeks post randomisation, because this was the period over which the primary outcome was measured.

4.3.7.3 Other permitted interventions

Patient's underlying malignancy was managed according to best practice as determined by standard care guidelines and the local oncology multi-disciplinary teams.

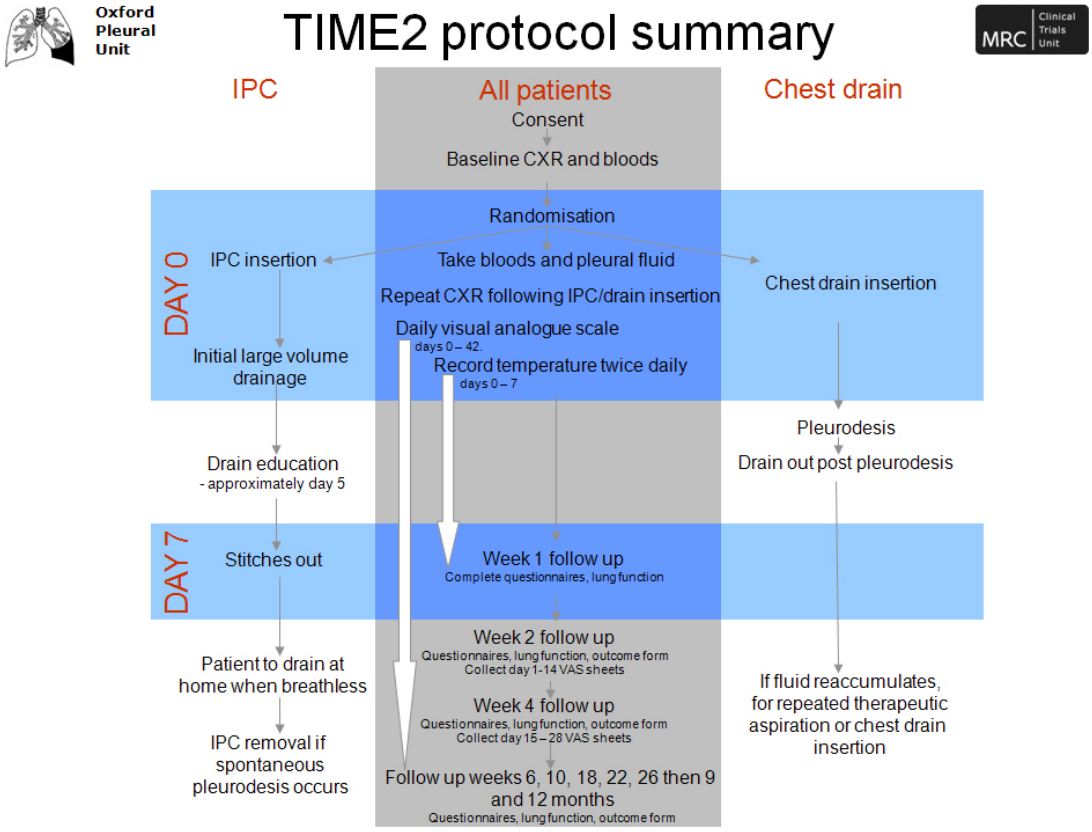
No medications or treatments were disallowed and treatment was guided by clinical need.

Patients were not permitted to be entered into any other clinical trial for the duration of the trial i.e. 1 year from randomisation.

4.3.8 Protocol flow chart

Figure 4-1 summarises the trial protocol.

Figure 4-1: Summary of TIME2 trial protocol



4.3.9 Trial assessments

Baseline assessments were performed before any intervention and consisted of 100mm VAS scores for dyspnoea intensity, dyspnoea unpleasantness, chest pain intensity and chest pain unpleasantness, blood and pleural fluid sampling, health questionnaires (Chronic Respiratory Disease Questionnaire (CRDQ), EuroQol 5-dimensions questionnaire (EQ-5D) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30), Appendix C) and spirometry. To assess dyspnoea and chest pain unpleasantness, patients were asked 'On average, how much has your breathlessness/chest pain bothered you today?' Blood tests performed were full blood count, urea and electrolyte levels, C-reactive protein

levels and liver function tests. Pleural fluid tests performed were total protein level, lactate dehydrogenase, pH and glucose.

Baseline CXR had already been performed in all cases in order to diagnose the presence of a pleural effusion and these CXRs were collected. Percentage opacification of the hemithorax was measured by two independent researchers, who made a best estimate of the position of the hemidiaphragm and mediastinum. They then digitally outlined the entire hemithorax and the pleural effusion and calculated the area these represented. This method of assessing pleural fluid volume has been validated in previous studies[141]. The mean percentage measurement was recorded in order to assess whether the 2 groups had similar volumes of pleural fluid at baseline.

All subjects completed a diary consisting of daily VAS scores assessing dyspnoea intensity, dyspnoea unpleasantness, chest pain intensity and chest pain unpleasantness over the past 24 hours for 42 days. Patients were requested to complete the VAS diary at approximately the same time each day. Temperature was recorded twice daily for the first 7 days. Patients were provided with a thermometer to measure their own temperature at home.

Subjects were followed up at 1,2, 4, 6, 10, 18, 22 and 26 weeks, and 9 and 12 months or until death. Follow up was performed by the local research nurse either in the outpatient setting, at the patient's home or in hospital, with repeat VAS scores, questionnaires, spirometry and assessment of complications and health care utilisation.

4.3.10 Trial outcomes

4.3.10.1 Primary Outcome

The primary outcome was the mean daily dyspnoea intensity score over 42 days measured by a 100mm VAS as described above. The VAS was scored by measuring from 0mm ('not breathless at all') to the mark made by the patient. The VAS was measured to the nearest 0.5mm. If the patient had drawn a thick scribble across the line, then the middle of the mark was the point measured to. If the patient had made 2 marks across the line (and not clearly marked that one was an error), then the average distance between the 2 marks was recorded. If the patient had marked with a cross or arrow, then the intersection of the cross or the point of the arrow was taken as the point to be measured to. If the patient had made a mark that did not cross the line, then a line perpendicular to the 100mm line was drawn from the patient's mark, and the point this crossed the line measured to.

All VAS scores were measured twice by 2 independent researchers and the mean for each day was taken. If the 2 measurements differed by more than 3mm, both measurements were repeated by the same observers. The VAS diary sheets for IPC patients also had space for the patients to record whether they had drained that day and so the researchers measuring the VAS scores were not blinded to treatment arm.

4.3.10.2 Secondary Outcomes

The secondary outcomes were:

a) **VAS scores measured over first 42 days:**

   a. Dyspnoea unpleasantness
   b. Chest pain intensity.
   c. Chest pain unpleasantness.

The difference between intensity and unpleasantness was explained to the patients as follows: 'If you are feeling very breathless/in a lot of pain but you don't want to do anything that day, then it wouldn't bother you as much as if you had a lot too do that day, but couldn't because of the breathlessness/pain'. The question in the diary for dyspnoea unpleasantness was 'How much has your breathlessness bothered you today?' and the VAS was anchored with 'no bother at all' at 0mm and 'worst possible bother' at 100mm. The question in the diary for chest pain intensity was 'on average how much chest pain have you had today?' and the VAS was anchored with 'no pain at all' at 0mm and 'worst possible pain' at 100mm. The question in the diary for chest pain unpleasantness was 'How much has your chest pain bothered you today?' at the VAS was anchored with 'no bother at all' at 0mm and 'worst possible bother' at 100mm.

b) **Proportion of patients achieving clinically significant decrease in mean VAS over first 42 days**:

   a. Dyspnoea intensity (10mm)[116]
   b. Chest pain intensity (13mm)[183]

This information is important to clinicians because it helps them apply the study results to their patient cohort.

c) **VAS scores calculated at 6 weeks, 3 months and 6 months**:

a. Dyspnoea intensity
b. Chest pain intensity.

Although these scores were measured at other time points (10, 14, 18, 22 weeks and 9 and 12 months), it was decided to only compare these at 3 further time points, due to the likelihood of getting statistically significant results by chance when making multiple comparisons. Additionally, it was recognised that due to the high mortality of this patients, there would be very little data available at 9 and 12 months.

d) Self reported global quality of life assessed by EORTC-QLQ 30 (%) measured at 6 weeks, 3 and 6 months

A higher percentage on this scale represents a better quality of life. The minimal important difference is 7%[184].

e) Results of CRDQ at 6 weeks and 3 and 6 months

a. Total CRDQ score
b. Dyspnoea domain of CRDQ
c. Mastery domain of CRDQ

The minimal important difference is 10 for the total score, 2 for the mastery domain and 2.5 for the dyspnoea domain [117].

At the first time the questionnaire is administered, for the dyspnoea domain, the patients are asked to think of at least 5 activities which make them breathless. If they are unable to think of 5, then a list of activities is given to them for them to chose activities which make them breathless. These activities are recorded. They then chose the 5 most important activities from the list. They then report how breathless

these activities make them feel on a scale 1-7 (each point on the scale is associated with a phrase e.g. 'not at all', 'extremely'). The activities they selected on the first time the questionnaire was administered are used for every subsequent follow-up visit.

f) Proportion of patients with a fever (defined as a temperature > 37.5 degrees Celsius) during the first 7 days after randomisation.

g) **Length of hospital stay from randomisation to discharge** (day cases counting as 0 days).

h) **Total hospital stay related to pleural fluid drainage or drain-related complications**

All reported admissions were assessed by a blinded independent reviewer as to whether they were related to pleural fluid drainage or drain-related complications.

i) **All-cause mortality up to one year**.

j) Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) (ml) at 6 weeks and 3 and 6 months.

k) Proportion using oxygen, opiates or both at 6 weeks and 3 and 6 months.

l) Proportion treated with chemotherapy up to one year

m) Spontaneous pleurodesis rate in the IPC group

n) Further pleural procedures

o) Frequency and type of serious and non-serious adverse events.

All reported events were assessed by a blinded independent reviewer as to whether they were related to pleural fluid drainage or drain-related complications, whether they constituted adverse events, and if they were adverse events, whether they were serious by regulatory criteria.

4.3.10.3 Subgroup analyses

Two subgroup analyses was planned prior to analysis:

1. **Comparing patients who were inpatients at randomisation with those who were outpatients**. The rationale for choosing this subgroup analysis was that one of the advantages of IPCs is that management is as an outpatient. If the patient is an inpatient due to breathlessness from their effusion prior to drain insertion, then insertion of an IPC may allow more rapid discharge. However, if the patient is an inpatient for other reasons then insertion of an IPC would not aid discharge and one of the major benefits of an IPC is lost.

   The following outcomes were analysed in this subgroup:

   - Mean VAS dyspnoea over 42 days
   - Initial and total length of stay

2. **Assessing patients who survived less than 6 weeks**. The rationale for choosing this subgroup analysis was that one previous health economic analysis found that IPCs were more cost effective in patients surviving less than 6 weeks, but were less cost effective in patients surviving longer than 6 weeks[176]. However, traditionally IPCs have been reserved for patients with

better prognosis as it has been felt that these patients benefit more from IPCs and are better able to manage them.

The following outcomes were analysed in this subgroup:

- Mean VAS dyspnoea over 42 days
- Initial and total length of stay
- Pleurodesis success
- Frequency and type of adverse events.

4.3.11 Adverse events

All adverse events (AEs) occurring between day 1 and 14 following randomisation were recorded on routine CRFs. An AE was defined based on regulatory criteria as 'any untoward medical occurrence in a patient or clinical investigation subject administered a treatment but which does not necessarily have to have a causal relationship with this treatment.'

After the initial 14 days only the following adverse events were recorded on CRFs:

- Pleural infection
- Drain site/wound infection (local cellulitis)
- Pleural fluid recurrence
- IPC blockage
- Catheter tract metastases (tumour deposition at sites of pleural intervention)
- Any other event of medical interest as judged by the assessing clinician.

Only these related AEs were recorded because this was a patient group with a terminal disease who would experience many AEs during the time they were enrolled in the trial, the majority of which were not related to the trial interventions.

Serious adverse events (SAEs) are defined as any AE that:

- Results in death except for any death that is unequivocally due to progression of disease;
- Is life-threatening (i.e. with an immediate, not hypothetical, risk of death at the time of the event);
- Requires inpatient hospitalisation or prolongation of existing hospitalisation, excluding planned readmission for repeat drainage;
- Results in persistent or significant disability or incapacity; or
- Is a congenital anomaly/birth defect.

Expected SAEs included at 20% mortality at 3 months from the underlying malignancy, and this was reported on the patients' CRF for the next scheduled trial follow up visit and not reported as an SAE.

When SAEs were reported, they were graded as either resolved, persisting, worsened or fatal. SAEs were assessed at the time of reporting by an unblinded researcher as to whether they were related to the pleural intervention or not.

All AEs were assessed by a blinded researcher at the time of study analysis as to whether they were serious or not and whether they were related to the trial interventions. Only related AEs are reported here.

4.3.12 Statistical Analysis Plan

The statistical analysis plan was finalised prior to any assessment or analysis of data.

Analyses were undertaken on an intention-to-treat basis, and all randomised patients on whom an outcome was available were included in the analysis. All analyses were pre-planned prior to any data analysis unless specifically stated. All analyses were adjusted for the minimisation variables (performance status and tissue diagnosis)[185]. Stata version 12.1 and SPSS version 20.0.0 were used.

The difference between treatment arms in mean daily dyspnoea and chest pain VAS score over 42 days was calculated using a mixed-effects linear regression model. This approach was used to account for days with missing VAS scores (the analysis did not differentiate between scores missing due to patient death and those missing because the patient did not complete their VAS score on that day). Study day was modelled as a continuous variable using fractional polynomials and was included in the model as a random effect. The model adjusted for the baseline VAS score and mean imputation was used for patients on whom a baseline score was unavailable[186].

A number of sensitivity analyses were performed to ensure robustness of the primary analysis. A complete case analysis was performed, where the mean VAS score over 42 days was calculated for each patient (days with missing VAS scores were ignored). Results were analysed using a linear regression model. Next, multiple imputation was used to account for days with missing VAS scores. Follow-up was divided

into six one-week periods, and mean dyspnoea intensity was calculated for each period. If more than 3/7 VAS scores were missing in a period, the mean dyspnoea intensity was set to missing. Multiple imputation using chained equations was then used to impute periods with missing VAS scores. 50 imputations were used, and results were combined using Rubin's Rules. The imputation model included the mean VAS score in each follow-up period, and imputations were done separately by treatment groups.

A number of sensitivity analyses assessed robustness to departures from the missing-at-random assumption. Multiple imputation was performed as above, however missing data were assumed to be missing-not-at-random. Missing-not-at-random data was imputed by first imputing missing-at-random data, and then adding a set amount *y* to each imputed outcome. The amount *y* that is added to the imputed values can be thought of as the mean difference in VAS score between patients with observed data and those whose data is missing (conditional on any other covariates in the imputation model). We used *y* values of -10, -5, 5, 10, and 20 (positive *y* values indicate patients with missing VAS scores had worse dyspnoea than those with observed scores, and vice versa).

All-cause mortality was to be analysed using a Cox regression model however preliminary investigations during data analysis showed that the proportional hazards assumption was violated. Analysis was therefore based on restricted mean survival time which does not make any assumptions regarding proportional hazards[187]. A Kaplan-Meier graph showed crossing hazards, so it was hypothesised that one

treatment may provide an early advantage whereas the other treatment may provide a late advantage. We therefore estimated treatment effects at 6 weeks and at 3, 6, 9, and 12 months.

4.3.13 Power Calculations

Power calculations were based on pilot data demonstrating a mean daily VAS dyspnoea score over 28 days of 14mm (SD 11) in 10 patients treated with an IPC compared to 21mm (SD 10) in 10 patients treated with standard care. In order to detect this difference (alpha 0.05 and power 90% assuming a group SD of 10) primary outcome data on a total of 90 patients were required. Initially, the loss to follow up was estimated conservatively to be 25%, therefore requiring 114 patients to be recruited. Due to slow recruitment, a blinded assessment of data completeness for the primary outcome was undertaken by the Trial Management Group following recruitment of 106 patients, and it was found that primary outcome data had been obtained in 93 patients, so the trial was halted at this point.

4.3.14 Data integrity

Data was recorded on an Excel spreadsheet. To ensure data integrity, all of the data entry was rechecked for the primary outcome and the adverse events by referring back to the source data. In addition, 10% of data from enrolment and randomisation forms was checked. Data was then cleaned by checking ranges.

4.3.15 Withdrawal of patients from the trial

Local PIs wishing to withdraw a subject from the trial were required to contact the CI for guidance, with all relevant details of reasons for withdrawal recorded on the SAE forms. Participants withdrawn from the study intervention at any point were requested to continue normal trial follow up, unless specific consent for follow up was withdrawn. For participants moving away from the recruiting centre, every effort was made for the participant to be followed up at another participating trial centre or for follow-up via the participant's general practitioner or by telephone and letter.

4.3.16 Oversight Committees

4.3.16.1 Trial Management Group

The Trial Management Group, responsible for the day-to-day running of the trial consisted of the Chief Investigator (initially Professor RJO Davies, later Dr Najib Rahman), the Trial Co-ordinator/Trial Clinical Fellow (Dr Eleanor Mishra), Key Investigator (Dr YCG Lee), Research Nurse (Mrs N. Crosthwaite) and the Trial Administrator (Mrs E Hedley).

4.3.16.2 Trial Steering Committee

The trial was overseen by a Trial Steering Committee (TSC) which consisted of an Independent Chairman, the Chief Investigator (initially Professor RJO Davies, later Dr Najib Rahman), Trial Co-ordinator (Dr Eleanor Mishra), Trial Statistician (Prof Andrew Nunn), Key Investigator (Dr YCG Lee), Independent Expert (Dr A Wilcock) and a Research Nurse (Mrs N Crosthwaite).

4.3.16.3 Independent Data Monitoring Committee (IDMC)

The role of the IDMC was to review unblinded data in order to advise the TSC if issues arose or new data was published from other relevant studies. The IDMC consisted of Professor Tim Peto (Chairman), an Independent Statistician, an Expert Member and the Trial Statistician (Prof Andrew Nunn).

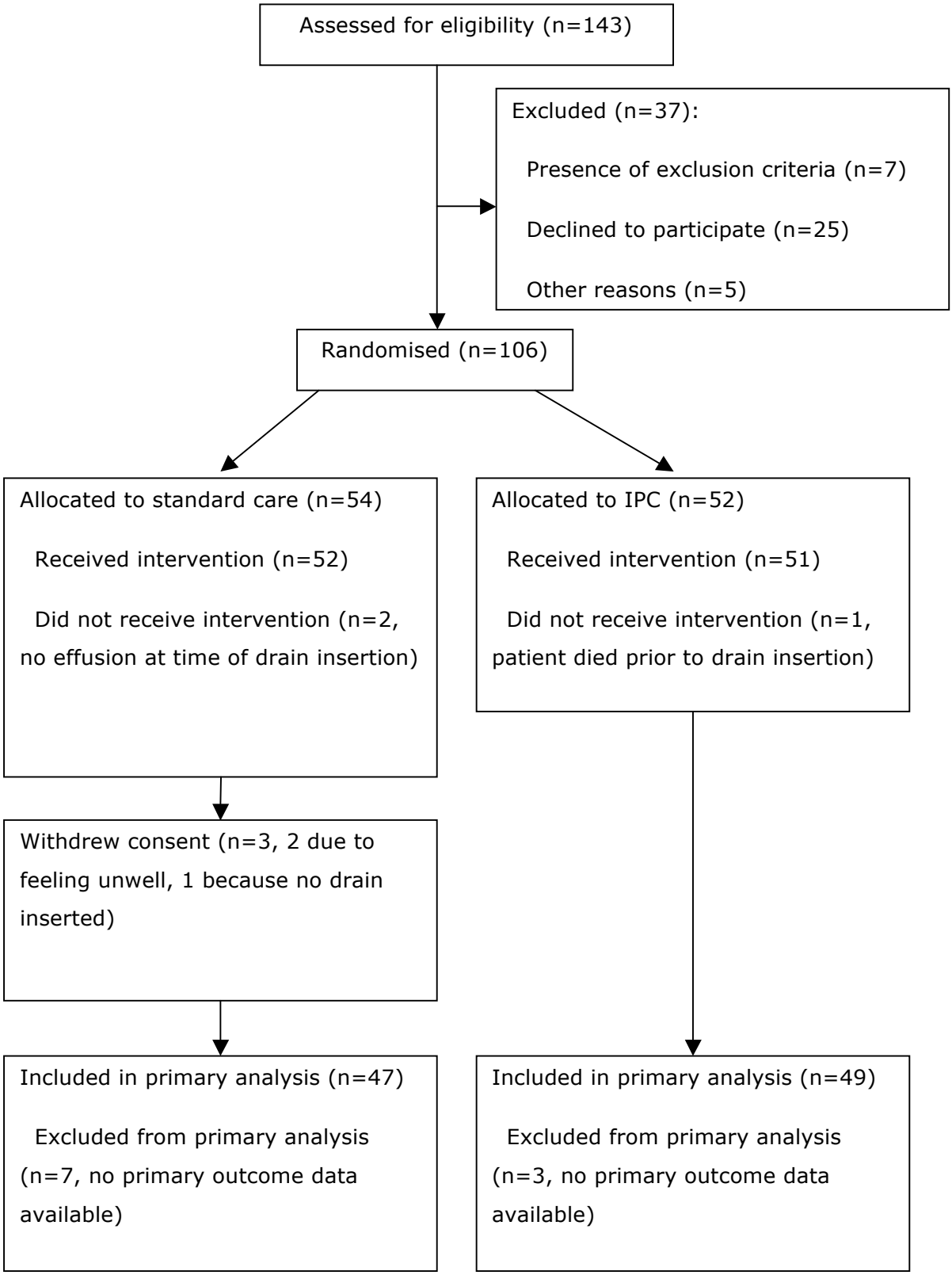
4.3.17 Ethical Approval and Registration

Ethical and regulatory approval for the study was obtained before recruitment commenced and the trial was registered (ISRCTN: 87514420).

4.4 Results

One hundred and six patients from 143 screened were recruited to the study between April 2007 and February 2011. The study was closed in February 2012 when the last patient completed follow up. Figure 4-2 is a CONSORT diagram summarising flow of patients through the study. The main reason recorded for most patients screened to not be enrolled was that they declined to participate because they would prefer to be treated with standard care rather than have an IPC inserted. Patients who did not give consent for enrolment were treated with standard care.

Figure 4-2 CONSORT diagram to describe patient flow through the trial

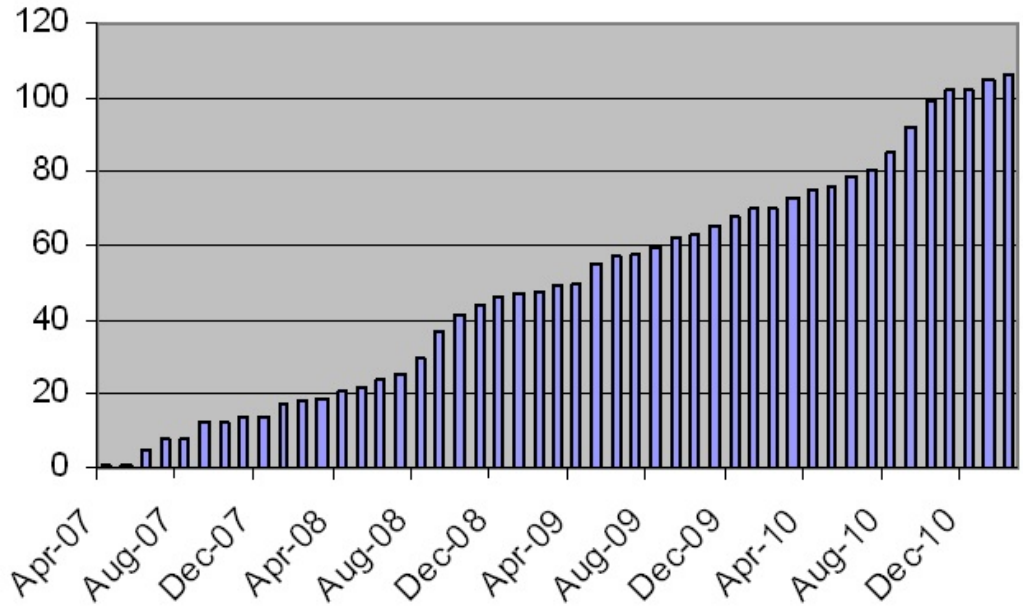


The number of patients recruited from the different sites was:

- Oxford University Hospitals NHS Trust: 82
- Buckinghamshire Healthcare NHS Trust: 2
- Great Western Hospital, Swindon: 6
- James Cook University Hospital, South Tees: 8
- Royal Berkshire Hospital, Reading: 6
- University Hospital of North Tees: 2

Figure 4-3 is a graph of number of patients recruited over time. The study was originally planned to complete recruitment of 114 patients over 24 months (mean 4.8 patients/month). Actual recruitment was 106 patients over 46 months (2.3 patients/month).

Figure 4-3: Number of patients recruited over time



All patients recruited at Oxford University Hospitals NHS Trust had their drain inserted immediately after randomisation. However, this was not possible in all other centres due to the logistical constraints of organising a hospital bed for the standard care patients and organising assistance and a procedure room for IPC insertion. Seven patients had a delay of at least 1 day between randomisation and drain insertion and enrolment (median 4 days, range 1-7 days).

Two patients in the standard care arm were thought to have a pleural effusion at the time of randomisation, but when an US was performed prior to drain insertion, they were found to have large volume of pleural metastases instead. One of these patients remained in trial follow up until their death 1 week later. The other withdrew consent for follow up once they found out they were not going to have a drain

inserted. Two other patients (both in the standard care group) withdrew consent, one due to a general deterioration following drain insertion and the second due to development of a needle phobia following randomisation but prior to drain insertion. One patient in the IPC group died at home between randomisation and enrolment/drain insertion.

4.4.1 Baseline demographics

Baseline demographic variables were generally well matched (Table 4-2). There were small differences in dyspnoea (mean VAS 62mm IPC vs. 55mm standard care), chest pain (mean VAS 29mm IPC vs. 22mm standard care) and in type of malignancy (breast 31% IPC vs. 20% standard care, lung 17% IPC vs. 30% standard care) and the percentage using opiates at enrolment (37% IPC vs. 19% standard care). All chest drains inserted in the standard care arm were 12 French.

Table 4-2: Baseline data for subjects enrolled into TIME2.

All figures are recorded to 2 significant figures. 1 patient in the standard care group died prior to enrolment so no enrolment data was available.

	IPC	**Standard care**	**Number missing data (IPC:Standard)**
Total	52	54	-
Mean age (years) (SD)	67 (11)	67 (12)	0

	IPC	Standard care	Number missing data (IPC:Standard)
Malignancy:			1 (0:1)
-breast	16	11	
-lung	9	16	
-mesothelioma	6	5	
-colorectal	4	3	
-ovarian	2	5	
-adenocarcinoma unknown primary	4	2	
-renal	3	2	
-sarcoma	1	2	
-thymoma	1	1	
-oesophageal	2	0	
-peritoneal	1	1	
-prostate	1	0	
-ampullary	1	0	
-leiomyosarcoma	1	0	
-melanoma	0	1	
-myeloma	0	1	
-masopharyngeal	0	1	
-unknown	1	1	
Male:female (%male)	23:29 (44)	23:31 (43)	0
Cytology positive v.	27:23	27:25	0

	IPC	Standard care	Number missing data (IPC:Standard)
negative			
Performance status (ratio 0-1:2-3) (% 0-1)	30:22 (58)	30:24 (56)	0
Receiving chemotherapy at enrolment (%)	8 (15)	5 (9)	
Using opiates at enrolment (%)	19 (37)	10 (19)	1 (0:1)
Using oxygen at enrolment (%)	9 (17)	6 (11)	1 (0:1)
FEV1 (ml) (SD)	1100 (400)	1200 (450)	7 (3:4)
FVC (ml) (SD)	1400 (540)	1500 (570)	6 (2:4)

	IPC	Standard care	Number missing data (IPC:Standard)
Mean baseline VAS dyspnoea intensity (mm) (SD)	62 (22)	55 (26)	11 (3:8)
Mean baseline VAS dyspnoea unpleasantness (mm) (SD)	60 (25)	50 (28)	11 (3:8)
Mean baseline VAS chest pain intensity (mm) (SD)	29 (30)	22 (29)	11 (3:8)
Mean baseline VAS chest pain intensity (mm) (SD)	27 (29)	23 (31)	11 (3:8)
Side of effusion right:left (% right)	27:25 (52)	32:20 (62)	2 (0:2)
Size of effusion (% hemithorax)	51 (23)	49 (25)	

	IPC	Standard care	Number missing data (IPC:Standard)
Mean baseline bloods:			
- Haemoglobin (g/dl)	13 (1.9)	12 (1.7)	3 (2:1)
- Urea (mmol/L)	6.1 (2.4)	8.1 (10)	6 (2:4)
- White cell count (*10^9/l)	9.8 (5.8)	9.8 (5.0)	3 (2:1)
- Platelets (*10^9/l)	340 (115)	350 (150)	3 (2:1)
- Albumin (g/L)	39 (5.3)	39 (3.9)	3 (1:2)
- C-reactive protein (mg/L)	52 (45)	72 (63)	16 (6:10)
- Prothrombin time (seconds)	14 (4.2)	14 (2.0)	17 (7:10)
- Activated prothrombin time (seconds)	29 (5.1)	28 (9.7)	12 (6:6)
Mean baseline pleural fluid:			
- Glucose (mmol/L)	6.3 (3.1)	5.0 (2.3)	10 (3:7)
- Lactate dehydrogenase (IU/L)	596 (850)	730 (840)	7 (3:4)
- pH	7.4 (0.22)	7.4 (0.26)	22 (11:11)
- Total Protein (g/L)	43 (7.8)	48 (42)	7 (3:4)

	IPC	Standard care	Number missing data (IPC:Standard)
EORTC: Values below are percentages (SD) 1 complete missing form (0:1). Numbers below are additional missing data to individual questions.			
Global health status/QoL	37 (23)	37 (20)	1 (1:0)
Physical functioning	45 (22)	45 (23)	4 (3:1)
Role functioning	26 (26)	23 (25)	0
Emotional functioning	66 (23)	61 (26)	4 (3:1)
Cognitive functioning	71 (32)	74 (29)	0
Social functioning	46 (33)	42 (33)	0
Fatigue	65 (25)	71 (25)	3 (3:0)
Nausea and vomiting	23 (26)	18 (27)	3 (1:2)
Pain	43 (35)	42 (35)	1 (1:0)
Dyspnoea	80 (24)	82 (23)	0
Insomnia	48 (35)	50 (37)	1 (1:0)
Appetite loss	58 (34)	64 (32)	0
Constipation	29 (39)	28 (30)	0
Diarrhoea	14 (25)	7 (17)	1 (1:0)
Financial difficulties	15 (28)	13 (26)	0
CRDQ: Score (SD)			
CRDQ total	13 (3.4)	13 (3.7)	3 (2:1)
CRDQ mastery	4.0 (1.2)	3.7 (1.2)	3 (2:1)

	IPC	Standard care	Number missing data (IPC:Standard)
CRDQ dyspnoea	2.6 (0.8)	3.0 (1.1)	3 (2:1)
Other data			
Inpatient:outpatient at enrolment (% inpatient)	19:33 (35)	22:31 (42)	1 (0:1)
Treatment prior to enrolment			
Chemotherapy	30 (58)	29 (55)	1 (0:1)
Radiotherapy	20 (38)	15 (28)	1 (0:1)
Surgery	15 (29)	12 (23)	1 (0:1)

4.4.2 Primary outcome

Ten patients (7 standard care and 3 IPC) had no follow-up data for the VAS scores, and were excluded from the analyses. One patient had missing data on baseline scores and mean imputation was used[186]. For each of the four VAS scores measured over 42 days, approximately 14% of data was missing (11% IPC, 17% standard care) excluding days after the patient had died. The median number of days with completed VAS scores over the first 42 days was 41 (IQR 15-42) in the standard care arm, and 41 (IQR 32.5-42) in the IPC arm. Table 4-3 summarises the completeness of data for the four VAS measurements.

Table 4-3: Summary of data completeness for VAS scores

	Usual care (n=54)	**IPC (n=52)**	**Overall (n=106)**
Number of days VAS scores are collectable over 42 days (e.g. days patient is alive)	1963	2091	4054
Dyspnoea intensity over 42 days			
Missing	342 (17%)	237 (11%)	579 (14%)
Completed	1621 (83%)	1854 (89%)	3475 (86%)
Scores observed per patient (median, IQR)	41 (15-42)	41 (32.5-42)	41 (28-42)
Number of patients with no observed scores (i.e. missing all 42 days)	7 (13%)	3 (6%)	10 (9%)

	Usual care (n=54)	**IPC (n=52)**	**Overall (n=106)**
Dyspnoea unpleasantness over 42 days			
Missing	341 (17%)	237 (11%)	578 (14%)
Completed	1622 (83%)	1854 (89%)	3476 (86%)
Scores observed per patient (median, IQR)	41 (15-42)	41 (32.5-42)	41 (28-42)
Number of patients with no observed scores (i.e. missing all 42 days)	7 (13%)	3 (6%)	10 (9%)
Chest pain intensity over 42 days			
Missing	342 (17%)	241 (12%)	583 (14%)
Completed	1621 (83%)	1850 (88%)	3471 (86%)
Scores observed per patient (median, IQR)	41 (15-42)	41 (32.5-42)	41 (28-42)
Number of patients with no observed scores (i.e. missing all 42 days)	7 (13%)	3 (6%)	10 (9%)

	Usual care (n=54)	**IPC (n=52)**	**Overall (n=106)**
Chest pain unpleasantness over 42 days			
Missing	342 (17%)	239 (11%)	581 (14%)
Completed	1621 (83%)	1852 (89%)	3473 (86%)
Scores observed per patient (median, IQR)	41 (15-42)	41 (32.5-42)	41 (28-42)
Number of patients with no observed scores (i.e. missing all 42 days)	7 (13%)	3 (6%)	10 (9%)

There were no significant differences between treatment arms in dyspnoea intensity (Table 4-4, Figure 4-4). Mean VAS dyspnoea in the IPC group was 24.7mm (SD 18.9) compared to 24.4mm (SD 17.0) in the standard care group (difference (IPC – standard care) 0.16, 95% CI -6.82 to 7.15, p=0.96). Given the IPC group had a higher baseline VAS score, the mean change from baseline was greater in the IPC group (mean change from baseline -30.2 (SD 27.7) in standard care, -37.0 (SD 27.1) IPC group). There was no evidence of an interaction between treatment and time.

Table 4-4: Mean VAS scores over 42 days

	Standard care mm (SD)	**IPC** mm (SD)	**Mean difference (IPC – Standard care)** mm	**95% CI**	**P-value**
Dyspnoea intensity	24.4 (17.0)	24.7 (18.9)	0.16	-6.8 – 7.2	0.96
Dyspnoea unpleasantness	22.7 (17.0)	23.6 (18.6)	2.1	-4.7 – 9.0	0.54
Chest pain intensity	17.6 (16.0)	20.5 (18.2)	5.4	-3.0-14	0.69
Chest pain unpleasantness	17.9 (16.8)	19.9 (17.7)	5.9	-2.4 – 14	0.17

Figure 4-4: Scatter plots of mean VAS scores between IPC and usual care groups.

Green circles represent individual subject's mean VAS score. Red line represents group mean.

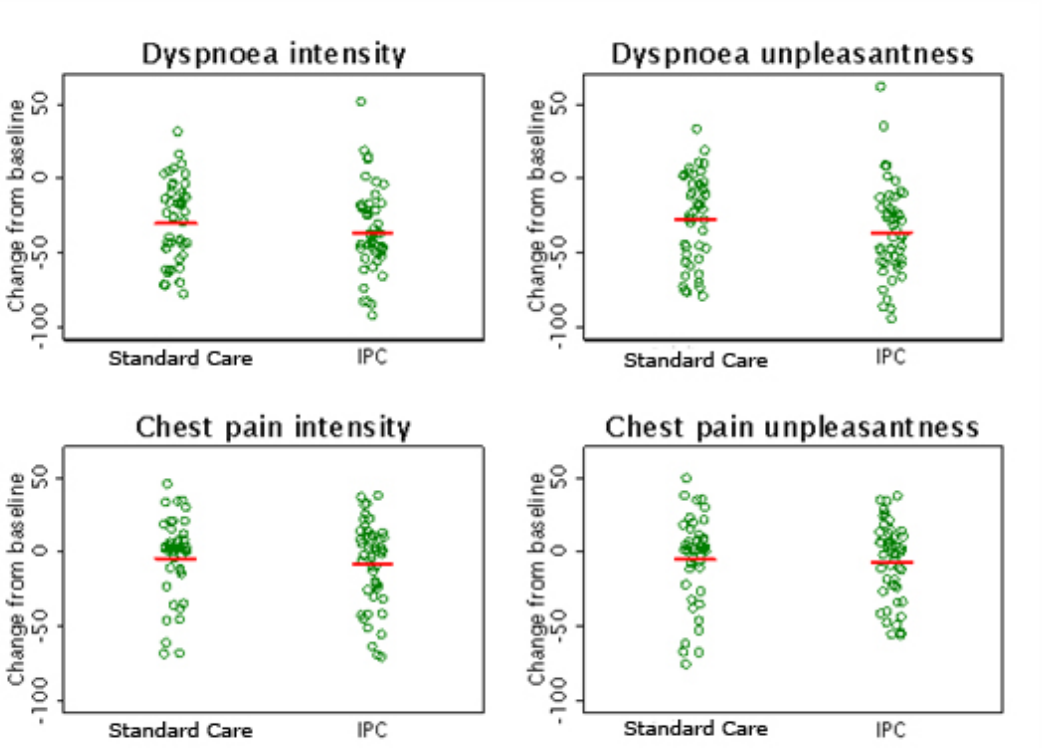
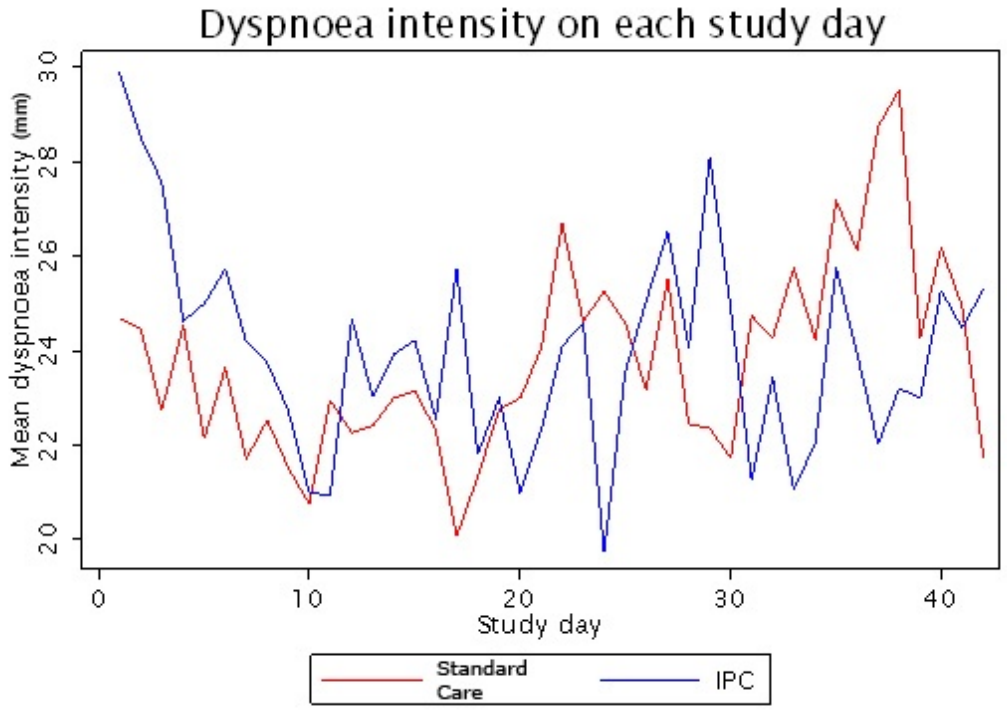


Figure 4-5 shows the mean value of dyspnoea intensity for each day for the 2 treatment arms over 42 days. A secondary analysis explored whether the treatment effect varied over time (Figure 4-6). It found during the first couple of study days, there was a non-significant trend to greater levels of dyspnoea in the IPC group but this rapidly dropped to zero and remained here for the remainder of the first 42 days of follow-up.

Figure 4-5: Mean VAS values for dyspnoea intensity over 42 days

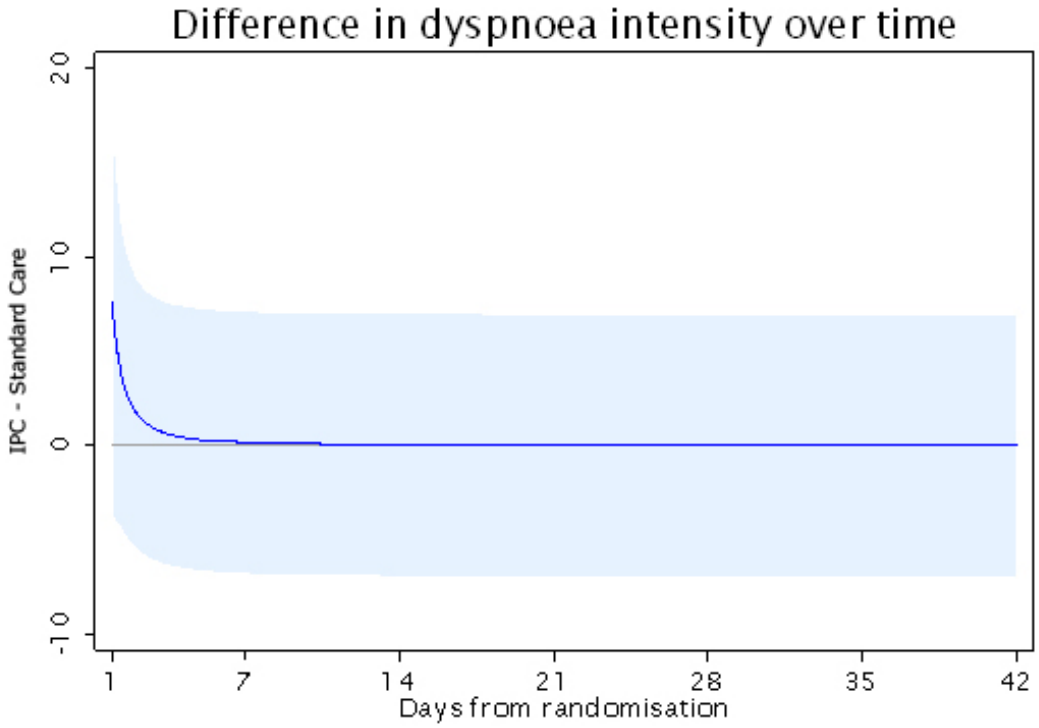


4.4.2.1 Primary outcome – sensitivity analyses

A complete case analysis showed no significant difference in dyspnoea intensity between treatment groups (difference (IPC vs talc) 0.1, 95% CI -7.0 to 7.2, p=0.97).

Using multiple imputation and assuming missing data were missing-at-random showed similar results (difference (IPC vs talc) -0.3, 95% CI -9.3 to 8.7, p=0.94).

Figure 4-6: Difference in mean VAS score for dyspnoea intensity over time between IPC and standard care groups



Results were similar under missing-not-at-random scenarios;

y=-10; (difference (IPC vs talc) 0.9, 95% CI -8.1 to 9.9, p=0.85)

y=-5; (difference (IPC vs talc) 0.3, 95% CI -8.7 to 9.2, p=0.95)

y=5; (difference (IPC vs talc) -1.0, 95% CI -10.1 to 8.1, p=0.83)

y=10; (difference (IPC vs talc) -1.6, 95% CI -10.8 to 7.6, p=0.73)

y=20; (difference (IPC vs talc) -2.8, 95% CI -12.4 to 6.8, p=0.56).

These results confirm that there was no significant difference in dyspnoea intensity between the two groups.

4.4.3 Secondary outcomes

4.4.3.1 Dyspnoea unpleasantness

Data completeness for dyspnoea unpleasantness was similar to that of the primary outcome. There was no significant difference in dyspnoea unpleasantness between the two groups (mean VAS 23.6mm (SD 18.6) IPC group compared to 22.7mm (SD 17.0) standard care group, difference (IPC – standard care) 2.14, 95% CI -4.70 to 8.97, p=0.54). Change from baseline was -27.0mm (SD 29.7) and -36.4mm (SD 29.1) in standard care and IPC respectively.

4.4.3.2 Chest pain

Data completeness for chest pain was similar to that of the primary outcome. There was no significant difference in chest pain intensity or unpleasantness between the two groups, with a mean VAS score of chest pain intensity over 42 days in the IPC group of 20.5mm (SD 18.2) and in the standard care group of 17.6mm (SD 16.0).

Non-significant decreases from baseline were found in chest pain intensity (change from baseline -4.4 (SD 27.6) and -8.2 (SD 27.6) in standard care and IPC respectively; difference (IPC – standard care) 5.40, 95% CI -2.98 to 13.77, p=0.21), and chest pain unpleasantness (change from baseline -5.1 (SD 29.7) and -7.1 (SD 24.9) in standard care and IPC respectively; difference (IPC – standard care) 5.88, 95% CI -2.44 to 14.20, p=0.17). However, a number of sensitivity analyses showed a much smaller effect.

4.4.3.3 Proportion of patients achieving clinically significant decrease in mean VAS over first 42 days

A 10mm decrease in mean VAS dyspnoea (considered at the time of writing the SAP to be a clinically significant decrease [116]) was observed in 42/49 (86%) patients in the IPC group and in 35/47 (74%) patients in the standard care group. This difference was not statistically significant (IPC vs. standard care OR 2.1, 95% CI 0.73 to 5.8, p=0.17).

A post-hoc reanalysis of the data using the value of 22mm as a MID as determined by the work in chapter 2, 36/49 (73%) patients in the IPC group had a clinically significant improvement in their dyspnoea compared to 24/47 (51%) in the standard care group. This difference was statistically significant (IPC vs. standard care OR 2.7, 95% CI 1.1 – 6.2, p=0.025). However, when this analysis was corrected for baseline VASD, it was found that treatment group no longer significantly predicted outcome (For IPC versus standard care, B=3.2, 95% CI 0.69-15, p =0.14).

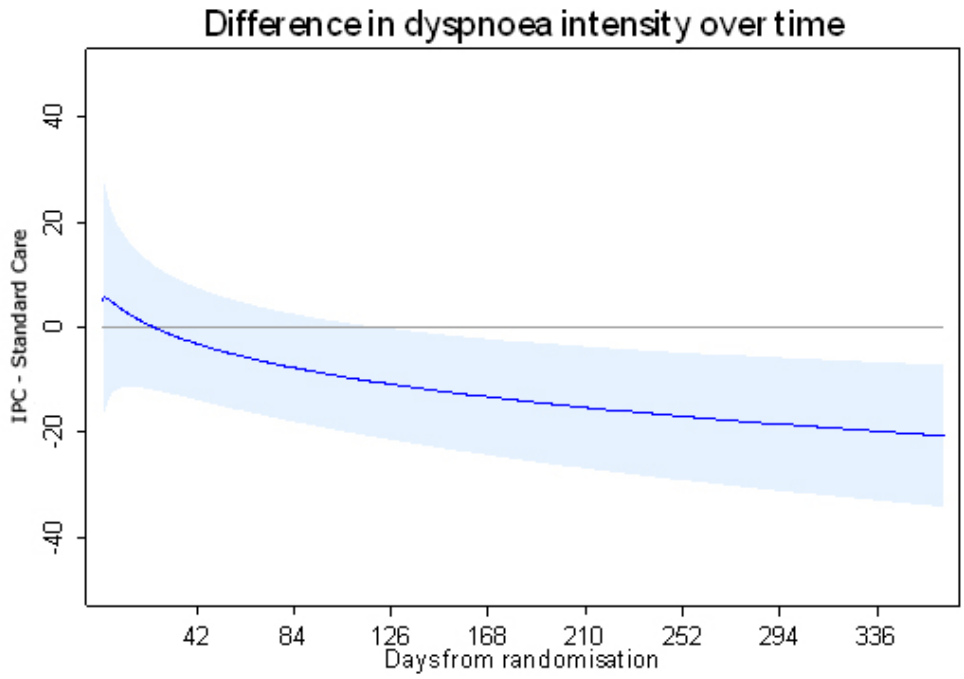
Twelve (26%) patients in the standard care group and 17 (35%) in the IPC group had a clinically significant improvement in chest pain intensity (13mm)[183] (OR IPC v. talc 0.75, p=0.77).

4.4.3.4 VAS scores calculated at 6 weeks, 3 months and 6 months

Follow up data showed 86, 69, and 54 patients were alive at 6 weeks, 3 months, and 6 months respectively, with 62, 57, and 43 patients having recorded VAS scores at these time points.

Linear regression modelling of dyspnoea after 6 weeks as described in the statistical analysis plan, showed was no significant difference in dyspnoea between the groups, until 6 months, at which point there was a clinically and statistically significant decrease in dyspnoea in the IPC group compared to the talc group (difference in mean VAS (IPC vs. talc) at 3 months = -8.9mm, 95% CI 1.7 to -19.4, p=0.10; at 6 months = -14.0mm, 95% CI -25.2 to -2.8, p=0.01) (Figure 4-7).

Figure 4-7: Difference in dyspnoea intensity over time. Linear regression model.
Light blue represents 95% confidence intervals.



No significant difference in chest pain intensity or unpleasantness was observed between groups for the duration of the trial, with difference in mean VAS (IPC vs. talc) at day 42 = 1.1mm, 95% CI -5.3

to 7.6, p=0.73; and 0.7mm, 95% CI -5.7 to 7.0, p=0.84, respectively. At 6 months = -0.6mm, 95% CI -15.2 to 14.1, p=0.94 and -0.3mm, 95% CI, -15.5 to 15.0, p=0.97, respectively.

4.4.3.5 Self reported global quality of life assessed by EORTC-QLQ 30

Follow up data showed 69, 56, and 41 patients had observed data at 6 weeks, 3 months, and 6 months respectively.

There was a clinically significant improvement (i.e. an improvement of 7% or more) in global quality of life measured by the EORTC QLQ-30 in both groups at 6 weeks but this only reached statistical significance in the IPC group (increase of 18.3 in IPC ($p<0.001$), 7.1 in talc ($p=0.15$)). At 6 weeks, mean global quality of life was 59% in the IPC group and 48% in the standard care group and this difference just reached statistical significance, but this should be interpreted with caution given that multiple statistical comparisons have been performed (**Table 4-5**). There was no significant difference in global quality of life at 3 or 6 months.

Table 4-5: Global health status as measured by EORTC in standard care and IPC groups at 6 weeks and 3 and 6 months

Time point	IPC mean (SD) %	Standard care mean (SD) %	Estimated difference (IPC – standard care) %	95% CI	P-value
6 weeks	59 (21)	48 (23)	11	0.06-22	0.049
3 months	55 (24)	60 (18)	-4.9	-16 – 6.1	0.37
6 months	62 (24)	59 (20)	2.1	-12 - 16	0.76

4.4.3.6 CRDQ

Overall score and dyspnoea and mastery domains improved in both groups from baseline, although these differences were only clinically and statistically significant in the dyspnoea domain of the IPC group (mean improvement in score 2.3, SD 1.8, 95% CI 1.7-2.9, $p<0.001$). There were no significant differences in total CRDQ score or dyspnoea or mastery domains between the two groups at any of the analysed time points (6 weeks, 3 months, 6 months). This data is summarised in Table 4-6.

Table 4-6: Results of CRDQ

Time point	IPC mean score (SD)	Standard care mean score (SD)	Estimated difference (IPC – standard care)	95% CI	P-value
	Total score				
6 weeks	19.4 (4.6)	17.5 (5.0)	0.9	-0.8 to 2.7	0.31
3 months	19.6 (4.6)	17.9 (4.5)	0.7	-1.2 to 2.6	0.47
6 months	20.4 (5.5)	18.9 (5.1)	0.4	-2.2 to 3.0	0.75
	Dyspnoea domain				
6 weeks	5.0 (1.6)	4.7 (1.8)	0.4	-0.2 to 1.0	0.22
3 months	5.1 (1.5)	4.7 (1.5)	0.3	-0.3 to 1.0	0.30
6 months	5.1 (1.9)	4.8 (1.8)	0.3	-0.5 to 1.1	0.49
	Mastery domain				
6 weeks	5.5 (1.1)	5.1 (1.4)	0.0	-0.5 to 0.5	0.95
3 months	5.5 (1.1)	5.0 (1.4)	0.0	-0.6 to 0.5	0.91
6 months	5.6 (1.2)	5.6 (1.3)	-0.1	-0.8 to 0.6	0.78

4.4.3.7 Length of hospital stay from randomisation to discharge

Overall, 51 patients (98%) in the IPC group and 48 patients (89%) in the talc group were included in the analysis (4 patients excluded due to lack of follow-up information (IPC 1, talc 3), and 3 patients excluded due to in-hospital mortality (all talc, died of underlying malignancy at 9, 9 and 13 days following randomisation).

The time from randomisation to discharge was significantly shorter in the IPC group (IPC median 0 days (IQR 0-1), talc 4 days (IQR 2-6); difference (IPC – talc) = -3.5 days, 95% CI -4.8 to -1.5, p<0.001).

4.4.3.8 Total hospital stay related to pleural fluid drainage or drain-related complications

Post hoc analysis showed no significant difference in the rates of readmission for repeat drainage or drain related complications between the study groups (IPC 23%, talc 16%; OR 1.59, 95% CI 0.52 to 5.08, p=0.51). There was a significant decrease in total number of days in hospital over 12 months in the IPC group for drainage or drain related complications (IPC median 1 (IQR 0-3), talc median 4.5 (IQR 2.5-7.5), p<0.001 (post-hoc analysis)). This data was heavily skewed, with 1 patient in the IPC group spending 73 days in hospital over 3 admissions for a pleural infection.

Patients randomised to IPC were more likely to be readmitted for complications (11 admissions for complications compared to 2 for pleurodesis failure) whereas patients randomised to standard care were more likely to be readmitted for pleurodesis failure (3 admissions for

complications compared to 9 admissions for pleurodesis failure) (p=0.005).

4.4.3.9 Fever in first seven days after randomisation

No follow up data was available on 18 patients (10 IPC, 8 standard care) for temperature, and were excluded from the analysis. The median number of recorded temperature readings over the first 7 days (14 possible temperature readings) was 11 (IQR 7-13) in the IPC group, and 8 (IQR 6-14) in standard care.

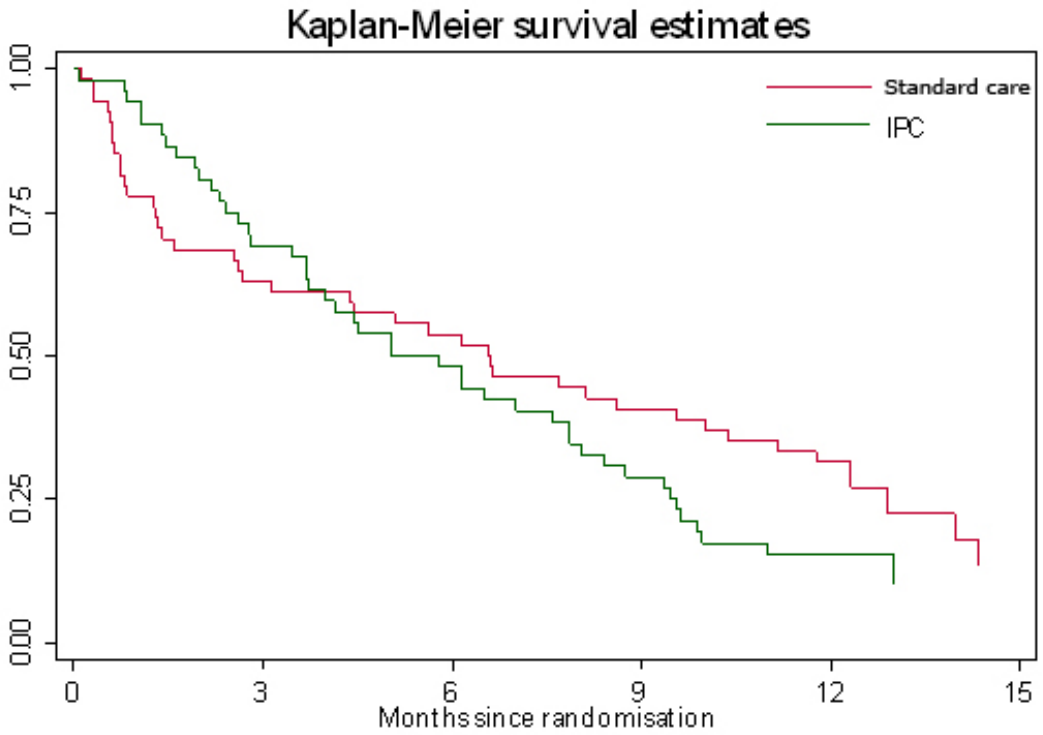
There was a non-significant trend towards increased fever during the first 7 days for patients in standard care compared to IPC (standard care 8/46 (17%), IPC 1/42 (2.4%); OR (IPC vs standard care) = 0.54, 95% CI 0.15 to 1.90, p=0.33).

4.4.3.10 All-cause mortality up to one year

Data were available for all patients. During the 1 year of follow up, 78 patients (74%) died (median duration of follow-up: 6.1 months (IQR 2.0 to 11.2)). 24 patients survived longer than 1 year, but mortality data after this time was available. Median survival time was 200 days (IQR 39-392) in the talc group and 153 days (IQR 73-288) in the IPC group. The Kaplan-Meier plot demonstrated crossing hazards (Figure 4-8) and there was strong evidence against the proportional hazards assumption (p=0.008). Post-hoc analysis using restricted mean survival time[187], adjusting for underlying malignancy type (breast vs. lung vs. other) showed a small but statistically significant increase in survival time in the IPC group up to 6 weeks compared to talc (difference (IPC – talc) 0.1 months, 95% CI 0.01 to 0.2, p=0.04). There

was a trend to improved survival in the talc group at 12 months, although this difference did not reach statistical significance (difference at 12 months (IPC – talc) -0.8 months, 95% CI -2.4 to 0.8, p=0.32 respectively).

Figure 4-8: Kaplan-Meier survival time estimates



4.4.3.11 FEV_1 and FVC at 6 weeks, 3 and 6 months

Patients in the standard care group were missing more data than in the IPC group, with a median number of spirometry measurements of 5 (IQR 3-9) in the IPC group compared to 3 (IQR 0-7) in the standard care group. Review of the CRFs showed that patients commonly declined performing spirometry because they felt too unwell to perform it. There was no significant difference in FEV_1 or FVC between the groups at any time point (Table 4-7). FEV_1 and FVC improved in both groups over time.

Table 4-7: FEV1 and FVC results in standard care and IPC groups at 6 weeks and 3 and 6 months

Time point	IPC mean (SD)	Standard care mean (SD)	Estimated difference (IPC – standard care)	95% CI	P-value
	FEV_1				
6 weeks	1.4 (0.5)	1.4 (0.6)	0.0	-0.1 to 0.2	0.66
3 months	1.5 (0.6)	1.4 (0.6)	0.0	-0.1 to 0.2	0.72
6 months	1.6 (0.6)	1.6 (0.6)	0.0	-0.2 to 0.3	0.83
	FVC				
6 weeks	1.8 (0.7)	1.8 (0.8)	0.1	-0.1 to 0.3	0.48
3 months	2.0 (0.8)	1.9 (0.8)	0.1	-0.2 to 0.3	0.65
6 months	2.1 (0.9)	2.2 (0.6)	0.0	-0.3 to 0.3	0.91

4.4.3.12 Proportion using oxygen, opiates or both at 6 weeks and 3 and 6 months

Data completeness was similar in the two groups, with a median number of assessments of 5.5 (IQR 1-9) in the IPC group compared to 6 (IQR 3-9) in the standard care group.

There was no significant difference between the groups in the proportion of patients using oxygen, opiates or both at the 3 time points assessed (Table 4-8). In patients in whom data was available at both time points, there was an overall increase in the proportion of patients using opiates from baseline to 42 days (increase from 12/44 (27%) to 15/44 (34%) in the IPC group and increase from 5/38 (13%) to 13/38 (34%) in the standard care group). There was a decrease in the proportion of patients with IPCs using oxygen but a small increase in the proportion of patients in the standard care group using oxygen (8/44 (18%) to 4/44 (9%) in IPC group, 6/38 (16%) to 8/38 (21%) in standard care group).

Table 4-8: Proportion of patients using opiates, oxygen or both at 6 weeks, 3 and 6 months

Time point	IPC n (%)	Standard care n (%)	OR (IPC vs standard care)	95% CI	P-value
	Opiates				
6 weeks	15 (34)	13 (34)	2.28	0.34-15	0.39
3 months	10 (30)	11 (38)	1.24	0.20-7.7	0.82
6 months	6 (25)	7 (30)	0.50	0.07-3.5	0.48
	Oxygen				
6 weeks	6 (14)	8 (21)	0.81	0.09-7.0	0.85
3 months	3 (9)	3 (10)	0.50	0.07-3.8	0.51
6 months	3 (13)	2 (9)	0.25	0.03-2.1	0.19
	Opiates or oxygen				
6 weeks	17 (39)	16 (42)	2.27	0.31-16	0.42
3 months	11 (33)	12 (41)	1.14	0.17-7.8	0.89
6 months	6 (25)	7 (30)	0.41	0.05-3.1	0.38

4.4.3.13 Proportion treated with chemotherapy up to one year

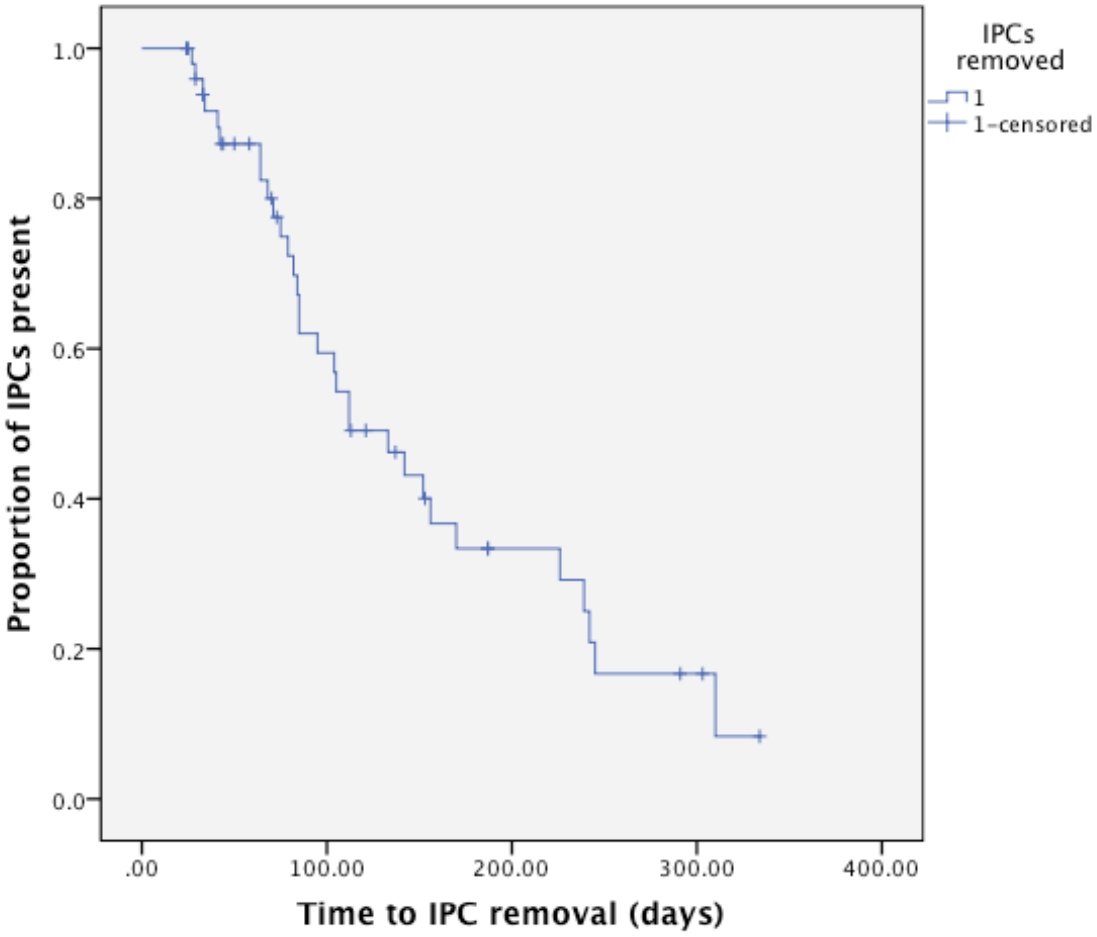
Data was available in 99 patients. The 9 patients in whom data was not available were all standard care patients. 13/52 (25%) patients had chemotherapy in the IPC group compared to 16/45 (36%) in the standard care group (odds ratio = 0.6, p=0.26).

4.4.3.14 IPC drainage, pleurodesis success and spontaneous pleurodesis rate

Mean number of 600ml drainage bottles used during initial IPC drainage was 3 (range 1-7). Mean IPC drainage frequency in the first 42 days was twice weekly.

A total of 29/51 (57%) IPCs were removed, however three (6%) patients subsequently required further pleural intervention (1 therapeutic aspiration, 2 chest tube insertions), giving an overall spontaneous pleurodesis rate of 51%. Median time to IPC removal was 95 days (range 27-310). Figure 4-9 summarises time to IPC removal with censoring of patients who died with their IPC in situ.

Figure 4-9: Kaplan-Meier curve of IPC removal with censoring of patients who died with their IPC in situ.



The mean volume of pleural fluid drained by the standard care group during the initial procedure was 3200ml (range 500-12000ml, SD 2200ml), but data was only available for 31 patients.

In the talc group, 6 patients were not pleurodesed, 3 due to trapped lung and 3 due to chest tube displacement. Twelve (22%) talc patients had further pleural procedures compared with 3 (6%) of the IPC group (OR of further procedures (IPC vs. talc) 0.21, 95% CI 0.04 to 0.86, p=0.03). The further pleural procedures were: therapeutic

aspiration (7 patients, 3 of whom had multiple pleural aspirations (4, 9 and 18 aspirations); repeat chest drain insertion (8 patients); and IPC insertion (2 patients).

4.4.3.15 Adverse events

The frequencies of serious and non-serious adverse events are summarised in Table 4-9. There was a statistically significant increase in the number of patients experiencing adverse events in the IPC group (IPC 21/52 (40%), talc 7/54 (13%), odds ratio (IPC vs. talc) 4.70, 95% CI 1.75 to 12.60, p=0.002). There was no significant difference in the rate of serious adverse events (IPC 9/52 (17%), talc 4/54 (7%), OR 2.81, 95% CI 0.75 to 10.55, p=0.13).

Table 4-9: Summary of adverse events by treatment groups

	IPC		Talc	
Type of adverse event	**Serious**	**Non-serious**	**Serious**	**Non-serious**
Pleural infection	5	2	1	0
Cellulitis	1	5	0	1
Symptomatic fluid loculation requiring fibrinolytics	1	2	1	0
Catheter site metastases	0	1	0	0
Catheter blockage	1	9	1	0
Other	1	0	2	3
Total	**9**	**19**	**5**	**4**

IPC blockage was the commonest adverse event, occurring in 11 patients. Nine cases required intrapleural fibrinolytics and 2 were treated with saline flushes alone. The IPC blockage considered serious by regulatory criteria was a patient who required hospital admission for breathlessness, because they had been unable to drain the IPC for 2 weeks, coupled with disease progression. All other blockages were managed as day case unit attendances alone. The case of catheter

blockage in the standard care group was observed in a patient who had had an IPC inserted following pleurodesis failure.

Eight pleural infections were reported, 7 in the IPC group and 1 in the standard care group. Two patients reported as having non-serious pleural infections were both asymptomatic and treated with oral antibiotics. Five other patients with pleural infection required admission for intravenous antibiotic treatment. One patient developed a pleural infection which necessitated 3 hospital admissions for intravenous antibiotics and intrapleural saline washes totalling 73 days as an inpatient and was discharged home twice on long term home intravenous antibiotics. This infection was considered contributory to the patient's death. All serious pleural infections occurred late (50, 63, 102, 114 and 206 days after IPC insertion). One patient was taking sunitinib at the time of infection but no other patients were on chemotherapy. None of the IPCs were removed because of the infection. Three patients went on to have a spontaneous pleurodesis.

Seven patients developed local cellulitis at the site of drain insertion. One of these patients had been admitted for an unrelated problem and noted incidentally to have redness around the IPC insertion site and was treated with 2 days of intravenous antibiotics, followed by oral antibiotics, so this was considered to be an SAE by regulatory criteria. The case of cellulitis in the standard care group was observed in a patient who had had an IPC inserted following pleurodesis failure.

Four patients developed symptomatic fluid loculation requiring intrapleural fibrinolytics. Fibrinolytics chosen were either streptokinase,

urokinase or alteplase. Two patients only had 1 dose of fibrinolytics and two had 5 doses over 5 days. The case of symptomatic fluid loculation in the standard care group was observed in a patient who had had an IPC inserted following pleurodesis failure.

One patient with renal cell carcinoma developed painful catheter site metastases which were treated successfully with radiotherapy.

Six 'other' adverse events were reported. Although chest pain was not considered an adverse event generally, because this was reported as a secondary outcome via the VAS diary, one patient in the IPC group was readmitted the night following IPC insertion with severe chest pain and required a 2 night hospital admission for pain control and this was considered an SAE. One patient in the talc group had a severely trapped lung and was readmitted the day following chest drain removal with surgical emphysema which was monitored in hospital for 2 days. One other patient in the talc group had a persistent air leak which prolonged his hospital stay for 8 days and he was then discharged home with a flutter valve. The air leak sealed spontaneously and the drain was removed. Three additional patients in the talc group had chest drain displacement before pleurodesis. Of these, 2 did not require any further pleural interventions and 1 went on to have a chest drain which was unsuccessful due to the presence of loculated fluid so he went on to have a medical thoracoscopy and pleurodesis.

4.4.4 Subgroup analysis: inpatients and outpatients at enrolment

At the time of enrolment, 41 patients were inpatients (19 received an IPC and 22 received standard care), 64 were outpatients (33 received an IPC and 32 received standard care) and 1 patient died prior to enrolment. Mean VAS dyspnoea at baseline was 62mm (SD 23mm) in the inpatient group and 56mm in the outpatient group (SD 25mm). This difference was not statistically significant (95% CI -4.0 – 15.8mm, p=0.24). Mean VAS dyspnoea over 42 days was 28mm (SD 16mm) in the inpatient group and 22mm (SD 19mm) in the outpatient group. Again, this difference was not statistically significant (95% CI -1.5-13, p=0.12).

Comparing inpatients at enrolment, there was no difference in mean VAS dyspnoea over 42 days between patients who received IPCs and those treated with standard care (IPC group, mean VAS dyspnoea 30mm, SD 16mm; standard care group, mean VAS dyspnoea 26mm, SD 16mm; 95% CI -5.6 - 16mm, p=0.35). Comparing outpatients at enrolment, again there was no difference in mean VAS dyspnoea in the 2 treatment groups (IPC group mean VAS dyspnoea 21mm, SD 20mm; standard care group mean VAS dyspnoea 24mm; 95% CI -13 – 7.4mm, p=0.60).

Median initial length of stay in patients who were inpatients at enrolment was 3 days (IQR 1-7 days) compared to 0 days (IQR 0-3.5 days) in those who were outpatients at enrolment. Comparing patients who were inpatients at enrolment, median length of stay was 1 day (IQR

1-3 days) in those who received IPCs compared to 4 days (IQR 2.8-7 days) in those who were treated with standard care (difference IPC-standard care -1.7 days, 95% CI -5.7-2.4, p=0.41). Comparing patients who were outpatients at enrolment, median length of stay was 0 days (IQR 0-0 days) in those who received IPCs compared to 4 days (IQR 2-5 days) in those who were treated with standard care (difference IPC-standard care -4.5 days, 95% CI -5.7 - -3.2 days, p<0.001).

Median total length of stay in patients who were inpatients at enrolment was 3 days (IQR 1-7 days) compared to 2 days (IQR 0-5 days) in those who were outpatients. Comparing patients who were inpatients at enrolment, median total length of stay was 2 days (IQR 1-3 days) in those who received IPCs compared to 4 days (IQR 2-7 days) in those who were treated with standard care (difference IPC-standard care -1.7 days, 95% CI -6.4 – 2.9 days, p=0.46). Comparing patients who were outpatients at enrolment, median total length of stay was 0 days (IQR 0-1 days) in those who received IPCs compared to 4 days (IQR 2.3-6 days) in those who were treated with standard care (difference IPC-standard care -1.3 days, 95% CI -8.3 - 5.6 days, p=0.7).

4.4.5 Subgroup analysis: patients surviving less than 6 weeks

A total of 20 patients survived less than 6 weeks, of whom 6 were randomised to an IPC and 14 to standard care. Primary outcome data was only available in 13 of these patients. There was no significant difference in dyspnoea at baseline between the patients who survived less than 6 weeks (mean baseline VAS 66mm, SD 24mm) compared to

those surviving more than 6 weeks (mean baseline VAS 60mm, SD 24mm) (difference 8.9mm, 95% CI -24 – 5.7mm, p=0.22). There was also no significant difference in dyspnoea over 42 days between those who survived less than 6 weeks (mean VAS dyspnoea over 42 days 32mm, SD 16mm) and those who survived more than 6 weeks (mean VAS dyspnoea over 42 days 23mm, SD 18mm) (difference 8.9mm, 95% CI -19 – 1.0mm, p=0.076).

Comparing patients surviving less than 6 weeks, there was no significant difference in patients who were randomised to an IPC (mean VAS dyspnoea 32mm, SD 16mm) compared to those who were randomised to standard care (mean VAS dyspnoea 32mm, SD 17mm) (mean difference 0.52mm, 95% CI -21 – 22mm, p=0.96). However, outcome data was only available in 4 patients receiving and IPC and 10 patients receiving standard care. Similar results were found for patients surviving greater than 6 weeks (IPC group mean VAS dyspnoea 24mm, SD 19mm; standard care mean VAS dyspnoea 22mm, SD 17mm; mean difference IPC - standard care 1.8mm, 95% CI -6.2 – 9.8mm).

In terms of initial length of stay, in patients surviving less than 6 weeks, patients randomised to an IPC stayed a median of 0 days (IQR 0-0 days) whereas patients randomised to standard care stayed a median of 5 days (IQR 3-8.5 days, excluding 3 patients who died during this initial admission) (Mean difference IPC – standard care -6.4 days, p=0.002, 95% CI = -9.9 - -2.9 days).

Analysing total length of stay, in patients surviving less than 6 weeks, patients randomised to an IPC stayed a median of 1 days in

hospital (IQR 0-2 days) whereas patients randomised to standard care stayed a median of 6 days (IQR 3 – 14 days) (Mean difference IPC – standard care -6.5 days, p=0.005, 95% CI -11 - -2.4 days). This means that, in patients surviving less than 6 weeks, patients randomised to IPCs spent 3.6% of the remainder of their lives in hospital for drainage related procedures or complications of the drain whereas patients randomised to standard care spent 37% of this time in hospital.

In patients surviving less than 6 weeks, only 1 patient experienced pleurodesis failure and this was a patient in the standard care group. One patient in each group experienced a serious adverse event (IPC group – severe chest pain requiring readmission, standard care group – pleural infection) and 1 patient randomised to standard care experienced an adverse event (drain fell out prior to pleurodesis).

4.5 Discussion

This is the first randomised trial to directly compare indwelling pleural catheters with chest tube and talc slurry pleurodesis for initial treatment of symptomatic malignant pleural effusion, and to assess the key outcome of dyspnoea[131]. These results demonstrate that both strategies are highly effective treatments for relieving dyspnoea (with over 75% achieving a clinically significant improvement), and that there was no significant difference in the clinically important outcome measures of chest pain and quality of life between these treatments. As such, indwelling pleural catheters cannot be advocated as a superior treatment to talc pleurodesis for palliation of symptoms. However, other factors such as length of hospital stay, adverse events and the

inconvenience of on-going drainage may be important factors in patient and physician choice of initial treatment modality in malignant pleural effusion, and this study provides initial data on which to base some of these choices.

Current guidelines advocate chest drain and talc pleurodesis as first line therapy for malignant pleural effusion, with indwelling pleural catheters reserved for second line treatment or for those without complete lung re-expansion[1]. The results of this study suggest that both standard care and IPCs are effective initial treatments for symptom relief in malignant pleural effusion and so patients can be offered the choice of treatment, based on their attitude to staying in hospital, draining the IPC themselves and risks of pleurodesis failure and adverse events.

The secondary outcomes in this study suggest that there may be advantages to the use of IPCs. These include a significantly shorter initial and total duration of hospital stay for drainage and drain related complications, congruent with published non-randomised series[163]. Other advantages include a clinically significant improvement in dyspnoea in the IPC group at 6 months and a 16% absolute reduction in the proportion of patients requiring further pleural interventions over 12 months. These secondary results are encouraging but should be interpreted with caution as this study was not powered to definitively address these outcomes.

The potential advantages of IPCs are, however, associated with an increase in observed adverse events (OR 4.7) compared to talc

pleurodesis, including 5 patients with pleural infection (9.6%), meeting regulatory criteria for seriousness, compared to 1 (1.9%) in the talc pleurodesis group. The 2 non-serious pleural infections reported may have represented catheter colonisation rather than infection as both patients were asymptomatic.

Overall cost of these treatments will be an important factor in determining which treatments are offered in the future. Previous studies comparing talc with IPC treatment have suggested reduced initial costs for IPC treatment but potential increased community care costs[148, 176]. Cost analysis was not the primary purpose of this study; however, cost economic analysis of this data, including assessment of both in-hospital and primary care use, is currently in progress.

4.5.1 Baseline demographics

Generally, the groups were well matched at baseline. Significantly however, there was an imbalance in the number of patients with lung and breast cancer between the groups, with more patients suffering from lung cancer in the IPC group and more from breast cancer in the standard care group. Given that patients with breast cancer generally have a much better prognosis than those with lung cancer, this may have meant the IPC group did worse than expected. However, analyses corrected for this imbalance between the groups.

Additionally, the mean VAS dyspnoea intensity in the IPC group was 7mm greater than the standard care group at baseline. Since the primary outcome was mean VAS dyspnoea, not decrease in mean VAS dyspnoea, this imbalance at baseline will have affected our ability to

detect a benefit of IPCs at relieving breathlessness. The greater baseline dyspnoea in the IPC group is also demonstrated by a mean CRDQ dyspnoea score of 2.6 versus 3.0 in the standard care group, although this difference of 0.4 was not clinically significant. The group randomised to IPCs were also more likely to be using opiates at enrolment (37% versus 19% in the standard care group) and using oxygen at enrolment (17% versus 11%), both palliative treatments for the relief of breathlessness. These differences demonstrate that the IPC group were more breathless at baseline than the standard care group.

The IPC group were also experiencing more chest pain (mean VAS 29mm versus 22mm in the standard care group) and found their breathlessness and chest pain to be more unpleasant (mean VAS dyspnoea unpleasantness 60mm versus 50mm standard care group; mean VAS chest pain unpleasantness 27mm versus 23mm standard care group), again suggesting that this group was more disabled at baseline.

The baseline demographics are similar to other large published series or trials recruiting patients with malignant pleural effusions. The mean age was 67 years in our study compared to 62 in an RCT comparing talc poudrage and talc slurry sclerosis by Dresler et al. and 64 in Tremblay's case series[93, 158]. There was a greater proportion of female subjects in these three studies, because pleural effusion is common in patients with breast cancer. The commonest cancers in our study and in these other series were breast cancer, lung cancer and mesothelioma. The comparability of our demographics to other published studies suggests that our patients recruited are typical of

those treated with IPCs or talc pleurodesis in other centres, and are therefore widely applicable.

4.5.2 Primary outcome

The primary outcome measure of mean VAS dyspnoea over 42 days showed no significant difference between the groups, suggesting that both IPC and chest drain and pleurodesis are comparably effective treatments at relieving breathlessness. This result was confirmed by various sensitivity analyses. However, the study was not designed to demonstrate equivalence and it is possible that, with a larger sample size, it might be demonstrable that one treatment produces a statistically significant improvement in breathlessness compared to the other. However, the 95% CI for the difference between the two (-6.82 to 7.15) do not include the MID for the VASD (demonstrated to be 22mm in chapter 2) and therefore these results exclude a clinically important difference.

The study had primary outcome data on 96 patients, giving us a power of 81% to detect a 7mm difference between the two groups with alpha 0.05 and SD 17. The actual SD over 42 days was much greater (27), a factor which may have contributed to our failure to detect a significant difference in mean change from baseline in VAS scores over 42 days. In order to detect a difference of 7mm with alpha 0.05 and power 80%, with a SD of 27, 234 patients would have been required.

The mean VAS dyspnoea in the standard care group dropped more rapidly than in the IPC group. This is likely to be due to the more rapid drainage of fluid in the standard care group. In the IPC group,

there was an initial large volume drainage of approximately 1500ml (equivalent to 3 drainage bottles) and then up to 500ml was drained up to every other day, whereas in the standard care group the entire volume of pleural fluid was drained during the initial procedure (mean volume 3200ml). This result suggests that IPC patients would benefit from drainage of a larger volume of pleural fluid following the initial procedure, and a practical way of doing this is to insert IPCs in the morning and connect the IPC to sequential 2 litre drainage bottles and drain the fluid over the course of the day until drainage stops, allowing the patient home at the end of the day.

4.5.3 Secondary outcomes

4.5.3.1 Proportion of patients experiencing a clinically significant decrease in dyspnoea

These results show that both treatments are effective for the relief of dyspnoea, with 73% in the IPC group and 51% in the standard care group achieving the minimal important difference in the VASD based on a value of 22mm, as determined by the work in chapter 2. This result was statistically significant, suggesting that patients treated with an IPC are more likely to experience a worthwhile improvement in their dyspnoea than those treated with standard care. However, it is important to note that this was a post-hoc analysis and the original SAP used a value of 10mm for the MID and no statistically significant difference was found with this value.

A limitation of these results is that only 1 baseline measurement of dyspnoea was made, compared to 42 subsequent measurements of

dyspnoea and a more accurate result might be achieved by taking more than 1 baseline measurement of dyspnoea. However, given the severe breathlessness experienced by these patients, it would not be ethical to wait longer between consent and drain insertion just to achieve a more accurate measurement of baseline dyspnoea. In TIME3, a RCT comparing intrapleural fibrinolytics to placebo in patients with septated malignant pleural effusions, this problem is partially overcome by making 2 baseline measurement of VAS dyspnoea, 1 at the time of consent and 1 just prior to drug administration (about 1 hour apart). However, this solution is not ideal, and patients rightly question why they are being asked to complete the same question twice.

4.5.3.2 Dyspnoea after 6 weeks

Analysis of VAS dyspnoea scores after 6 weeks showed a trend towards a decrease in dyspnoea in the patients randomised to IPC compared to the standard care group. This difference became statistically and clinically significant at 6 months. This result should be interpreted with caution because it was a secondary outcome and only 43 patients had data available. The clinical relevance of this is unclear, given that the median survival in this patient group is approximately 3 months.

4.5.3.3 Dyspnoea Unpleasantness

The results for dyspnoea unpleasantness were very similar to those for dyspnoea intensity. Analysis shows that patients did not give different scores for dyspnoea unpleasantness and dyspnoea intensity. This suggests that although there is a theoretical difference between

these dimensions of dyspnoea, in practice, patients do not distinguish between these. The implication of this result for further trials assessing dyspnoea is that there is no additional value to measuring dyspnoea unpleasantness as well as intensity.

4.5.3.4 Chest pain

There was no significant difference in chest pain between the two groups, with both groups overall experiencing a non-significant decrease in chest pain. We expected the standard care group to experience more chest pain, particularly early in follow up, due to the pain of pleurodesis. No peak of chest pain was seen in the standard care group around the time of pleurodesis. This may be because this tends to be an acute severe pain which is rapidly treated with strong analgesia. Unfortunately, the date of pleurodesis and analgesia given at this time was not recorded, so it is not possible to accurately assess chest pain on the day of pleurodesis. Further studies need to be done to accurately assess pain of pleurodesis.

Another surprise was that average chest pain fell in both groups from baseline, despite the painful pleural procedures undergone by both groups. This may be because of the increase in opiate use seen in both groups but it is also possible that the presence of a large volume of pleural fluid causes previously unrecognised chest discomfort, and the relief caused by draining this outweighs the other painful procedures.

4.5.3.5 Chronic Respiratory Disease Questionnaire

This questionnaire appeared poorly responsive to the changes in breathlessness in this group of patients, with small changes seen despite

large changes in the VAS dyspnoea score. This is probably because the questionnaire was developed for measuring small changes in dyspnoea in patients with chronic respiratory diseases which are less responsive to treatment, rather than for measuring the large change in breathlessness seen following drainage of a MPE. This is because the patients chose activities which made them feel breathless at the point of enrolment when they were very breathless, so the activities chosen were those which required minimal exertion e.g. bending over. Once patients had had their fluid drained, they no longer felt any breathlessness on the activities they had previously chosen but still felt breathless on greater exertion e.g. walking uphill. The questionnaire was unable to assess this. Other problems we found with the questionnaire was that it was time consuming to administer, complex, not intuitive for the patients to answer (e.g. the scale was reversed for some questions) and the patients did not like using it. For these reasons, this questionnaire will not be used further in studies of dyspnoea in patients with MPE in our group.

4.5.3.6 Hospital stay

It is unsurprising that patients treated with an IPC have a shorter initial hospital stay than those treated with standard care, because IPC insertion does not require hospital admission whereas standard care does. This result has important implications for allocation of health care resources and cost effectiveness.

4.5.3.7 All cause mortality

Mortality results show the group of patients randomised to this trial had a better prognosis (median life expectancy 200 days in the standard care group and 153 days in the IPC group) than historical reports of patients with MPEs (mean life expectancy 90-120 days). This may be because patients with a poor prognosis (expected survival <28 days) were excluded from the trial and because cancer treatment has improved so patients can expect a better outcome.

Our results showed an initial small (0.1 months) but statistically significant mortality advantage to IPCs with a later trend to a mortality advantage in the standard care group. These results should be interpreted cautiously because multiple statistical tests have been performed and the study was not powered to assess mortality. Talc is known to cause systemic inflammation at the time of pleurodesis and ungraded talc is associated with deaths from ARDS[97, 146]. Graded talc was used in this study, which has not been associated with ARDS, but it is possible that it is associated with some excess mortality. There is some evidence in vitro that talc has anticancer effects. Studies have shown that talc induces apoptosis in mesothelioma cells and that it mediates angiostasis in MPEs via endostatin induction[188, 189]. It is therefore possible that the results seen are due to an early excess mortality in the standard care group due to systemic inflammation and a later anticancer effect of talc. Significantly, the previous RCT comparing IPCs with chest drain and pleurodesis used doxycycline as a pleurodesis agent and did not show any difference in mortality between the two

groups[160]. Further studies are indicated to further investigate this potential effect on mortality.

4.5.3.8 Pleurodesis rate

Median time to IPC removal in this study was 95 days, longer than any previously published series. This is likely to be due to our conservative approach to IPC removal, with a 6 week wait from cessation of drainage to removal, compared to immediate removal following cessation of drainage in other published series. Given this conservative approach, it is unsurprising that further pleural procedures were only performed in 6% of patients, compared to 13% in another series[158]. The overall spontaneous pleurodesis rate was 51%, comparable to other published series. This data suggests that leaving the IPC in for longer reduces the need for further pleural procedures, but does not affect overall pleurodesis rate.

4.5.3.9 Subgroup analysis: inpatients versus outpatients at enrolment

This subgroup analysis showed that there was no difference in terms of relief of breathlessness between patients who were inpatients at enrolment and those who were outpatients. However, amongst patients who were outpatients at enrolment, those who were treated with IPCs had a significantly shorter hospital stay than those who were treated with standard care. In comparison, amongst patients who were inpatients at enrolment, there was no significant difference in hospital stay between the 2 treatment groups, although numbers were small.

This shows that, in terms of length of initial hospital stay, IPCs were only advantageous in outpatients.

This analysis simplifies the situation. There are some patients who are inpatients only due to breathlessness secondary to their pleural effusion and treating this breathlessness with either an IPC or standard care will enable the patient to be discharged. In this situation, patients could be offered the choice of treatment. However, if the patient is an inpatient for other reasons and pleural fluid drainage will not allow the patient to be discharged then standard care may be a better treatment modality. Unfortunately, the reasons patients were admitted was not collected in the trial and so it is not possible to make definitive management recommendations based on the data available.

4.5.4 Subgroup analysis: patients surviving less than 6 weeks

There was no difference in baseline dyspnoea between patients surviving less than 6 weeks and those surviving more than 6 weeks, demonstrating that the degree of breathlessness at presentation is not a predictor of survival time. Surprisingly, the group of patients surviving less than 6 weeks were not significantly more breathless than those surviving more than 6 weeks over the first 6 weeks. I would expect patients who were dying from metastatic cancer to experience more breathlessness than those with a long survival but this was not the case. One factor contributing to this could be that the patients who were breathless and dying were too sick to complete their VAS scores and so the VAS diaries are not an accurate measure of breathlessness.

There was no significant difference in dyspnoea in patients surviving less than 6 weeks in those randomised to IPCs compared to those randomised to standard care, supporting the idea that IPCs are a comparable treatment modality to standard care for patients surviving less than 6 weeks.

Amongst patients surviving less than 6 weeks, those randomised to IPC spent less of their remaining life in hospital than those randomised to standard care, demonstrating that IPCs can help patients with poor prognosis spend more time at home prior to death. In this group of patients, adverse events from IPCs were uncommon, again strengthening the argument for using IPCs in this patient group.

However, the clinical implications of this subgroup analysis should be interpreted with caution, as numbers were small and it is difficult to assess survival at the point of deciding what treatment a patient should receive. Alternative subgroup analysis could have been comparing those patients with good PS (WHO 0-1) at baseline with those with poor PS (WHO 2-3), but it was decided not to do this because of the limitation of performing multiple statistical analyses.

4.5.5 Limitations

A major limitation of the trial was that patients and investigators were not blinded to the group the patient had been randomised to. Dyspnoea is a subjective experience and patients' perception of the treatment they had been assigned to may have biased their estimation of their dyspnoea. In general, patients were blind to the treatment group they had been assigned to when they completed the enrolment

questionnaires, but were then necessarily unblinded. It would theoretically have been better for the trial assessments to be completed by a researcher blinded to the study group, but staffing limitations meant this was not practically possible. Additionally, patients often used trial assessments as an opportunity to undergo pleural aspiration or to discuss problems with the IPC so it would be difficult to maintain blinding under these circumstances. The researchers measuring the VAS scores were not blinded to the trial group because the IPC diaries were different to those of the standard care arm, which could have introduced bias when measuring the primary outcome. Ideally, this should have been considered at the time of trial design and the diaries made to appear identical.

One drawback of the trial protocol was that drainage frequency was not specified and so different clinicians may have advised patients to drain at different frequencies. My own practice changed as the trial progressed: initially, I advised patients to drain when they felt breathless, as the aim of drainage was symptom relief. However, as my experience grew and a few of our patients who had the IPCs in for a long period of time developed empyemas, I felt that keeping the pleural space dry to allow spontaneous pleurodesis, catheter removal and hence prevention of empyema was more important and so I advised patients to initially drain three times weekly, and then decrease drainage frequency when the volume drained fell below 250ml/drainage. Most case series have specified that they advised patients to drain three times weekly.

An additional drawback was that no clear definition of spontaneous pleurodesis and guidance for IPC removal was made prior

to starting the trial. This was because at the time of setting up the trial, IPCs were thought of as a permanent drain, but now it is recognised that the high spontaneous pleurodesis rate allows many drains to be removed early, before complications of prolonged stay can develop. This meant that different clinicians may have used different criteria for deciding when to remove IPCs.

Randomisation refusal was a major problem limiting recruitment to the study. The two treatment modalities studied are very different and I found that patients had a strong preference for one or the other which limited recruitment because patients who preferred standard treatment could chose not to be enrolled in the trial and would then receive their preferred treatment. Standard treatment offered the advantage that treatment was sorted out in one hospital stay, even though it could be prolonged, whereas IPCs required on-going management and potentially further out-patient visits for teaching, collecting drainage bottles and ultimately removal of the catheter. In contrast, other patients preferred the outpatient management offered by the IPCs. The same problem was found by Demmy et al. whose struggled to publish their RCT because only 57 patients were recruited over 2 years out of a target of 530[162]. They commented 'The study was closed early due to slow accrual and this was attributed to randomisation refusal because after its presentation subjects preferred in roughly equal proportions to have either the inpatient or the outpatient management.' The advantage we had was that IPCs were only available to patients entering the trial and the majority of patients

who were randomised were keen that this was the treatment modality they received.

A further limitation was that no follow-up CXRs were performed as part of the protocol. IPCs are standard treatment for patients with trapped lung, so it would have been useful to look at the proportion of patients in each group with trapped lung and include this as a variable in primary analysis. However, the protocol did not state a requirement for patients to have a CXR once all the fluid had been drained. All patients did have a CXR following drain insertion, but in the majority of cases there was still residual fluid at this time and so it was not possible to assess for the presence of trapped lung. I attempted to find follow up CXRs performed at approximately 28 days following randomisation, to assess for the presence of trapped lung and the size of residual effusion, but found a lot of variation in the timing of the CXR. Additionally, I was unable to assess the relationship of the CXR to drainage of the IPCs in the IPC group, so it was not possible to retrospectively assess whether this was residual effusion or whether there was trapped lung.

4.5.6 Future directions

Alternative first line treatments for MPE not assessed in this study include surgical pleurodesis with decortication or medical thoracoscopy and talc poudrage. A previous study has shown no significant difference in pleurodesis failure rate between talc poudrage and talc slurry[93]. However, the relative dyspnoea relief associated with these treatments has not been assessed and this should be the subject of further study. There is also interest in giving patients pleurodesis agents via IPCs to

see if this can reduce adverse events and cost while maintaining patients as an outpatient.

4.5.7 Conclusion

Among patients with malignant pleural effusion and no previous pleurodesis, there was no significant difference between indwelling pleural catheters and standard care in relieving patient-reported dyspnoea. Indwelling pleural catheters reduce time in hospital, but are associated with an excess of adverse events. The results from this study provide evidence upon which discussion of relative risks and benefits of each treatment can be based - treatment choice is likely to depend on individual patients' attitude towards hospital stay, home drainage and relative adverse effects.

5 Conclusion

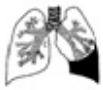
This thesis reports 3 interrelated studies. The first study was to determine the MID for the VASD demonstrated it to be 22mm (95% CI 16 – 27mm). This work has helped interpret results from TIME2 and allowed a reassessment of the power calculation for TIME3-UK, demonstrating that the study is currently overpowered.

The second study describes the development and validation of a TUSS. This work shows that a TUSS consisting of homogeneity of the effusion and septation number is a valid and reliable objective method of assessing degree of septation. Work on the MID for the VASD was used in this study to demonstrate that degree of septation is associated with dyspnoea relief following a pleural procedure.

The final study, TIME2, demonstrated that, in patients with MPEs, dyspnoea relief following IPC insertion was not significantly different from that following standard care.

Further work remains to be done to prospectively validate the TUSS with key clinical outcomes. One important outcome will be dyspnoea relief following therapeutic aspiration, for which the methods developed in Chapter 2 will be key. The TUSS will also be an important part of further work on TIME3-UK, a study of intrapleural fibrinolytics for the treatment of septated pleural effusions. Objective assessment of the degree of septation will help clinicians apply this work to their own practice.

6 Appendix A: Questionnaire for MID VASD



How has this drainage affected your breathing?

(a) On average how breathless have you felt the 24 hours before draining this fluid?

Not breathless at all ——— Worst possible breathlessness

(b) What is the smallest decrease in your breathlessness that you would consider worthwhile for this treatment?

Not breathless at all ——— Worst possible breathlessness

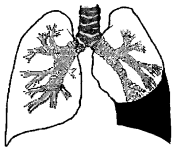
(c) On average how breathless have you felt the 24 hours after draining this fluid?

Not breathless at all ——— Worst possible breathlessness

(d) How much change have you noticed in your breathing after drainage of the fluid? Please tick 1 box.

Large or moderate deterioration	
Small but significant deterioration	
Slight deterioration but not significant	
No change	
Slight improvement but not worthwhile	
Small but just worthwhile improvement	
Large or moderate improvement	

7 Appendix B: Standard Operating Procedure for Talc Slurry Pleurodesis



SOP Title:	TIME 2
Author:	Dr E K Mishra
Reviewer:	
Authoriser:	
Version number and date:	Version 1.0 7th July 2010

7.1.1.1 Purpose:

To describe (1) when talc slurry pleurodesis is indicated for patient participating in the TIME2 trial and (2) how to administer talc slurry via the chest tube

Scope of this SOP: The scope of this SOP will relate to all patients participating in the TIME2 trial (who are undergoing talc pleurodesis)

Responsible personnel: Research doctors and doctors involved in care of the patients on the hospital ward

7.1.1.2 Procedure

Timing: When pleural fluid drainage is <150ml / 24hrs and / or when a good radiological result is seen (to be decided at the local clinicians discretion)

Data required:

- Chest X-ray – PA (and lateral if possible)
- Patient pleural fluid monitoring chart

7.1.1.3 Method

1. Discuss indication for talc pleurodesis with patient
2. Outline benefit of pleurodesis
    - Reduces likelihood of pleural effusion recurrence
3. Explain potential side effects
    - Fever, chest pain
    - Rarely respiratory failure as a result of adult respiratory distress syndrome
4. Obtain written informed consent
5. Consider pre-medication
    - Opioid analgesia: orally (e.g. oramorph 5-10mg) / intravenous (IV): 2.5-10mg morphine sulphate
    - Sedation: midazolam 1-2mg IV

    (Take care in the elderly patient and those with respiratory failure)

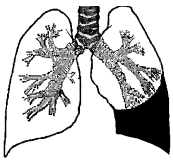
6. Prepare a trolley with
    - Procedure pack
    - 50ml Leur-lock syringe
    - 2 x 20ml Leur-lock syringes
    - 2 green needles
    - 60mls normal saline
    - 15ml 2% lignocaine local anaesthetic or 30mls 0.25% bupivucaine

- 4g sterile talc powder (high grade)

7. Administer intra-pleural local anaesthetic (15mls of 2% lignocaine)
8. Clamp drain and leave for 5-10 minutes – during this time prepare talc pleurodesis slurry by adding the 4g talc powder to 40ml of normal saline (use the 50ml syringe)
9. Administer sterile talc slurry followed by drain flush with the remaining 20ml normal saline
10. Clamp chest drain for 1 hour following talc slurry and then open and leave tube on free drainage
11. In the event of any increasing breathlessness during this one hour period, the drain may be unclamped and fluid allowed to drain off.
12. Apply suction starting at 5cm H_2O and increased incrementally to 20cm H_2O if tolerated by the patient over the following 4 hour period
13. Ensure analgesia is prescribed on the drug chart and tell patient to let nursing staff know if pain worsens or he/she feels more breathless
14. Ensure that VAS scores are collected by the patient

8 Appendix C: Questionnaires used in TIME2

These questionnaires used in TIME2 (EQ5D, EORTC and CRDQ) are reproduced over the following pages.



Centre No: 01

Patients Initials:

Patients Trial No:
REC No: 07/Q1603/2
ISRCTN87514420
EudraCT No: 2006-006630-18

RESPIRATORY TRIALS UNIT
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Tel: 01865 225205 Fax: 01865 857109

EQ-5D QUESTIONNAIRE

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

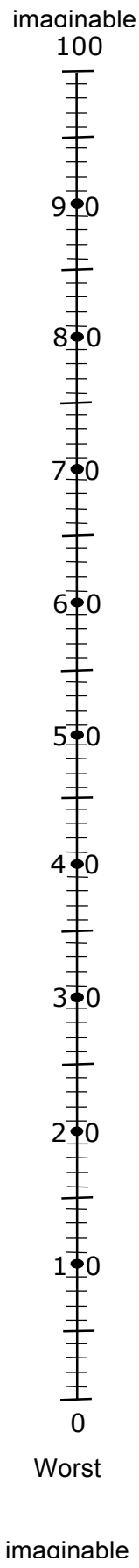
Anxiety/Depression

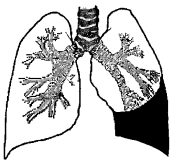
I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state





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THE EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE (EORTC QLQ C-30)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities like carrying a heavy shopping bag or suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:				
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4

13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhoea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

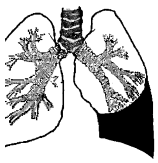
1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent



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CHRONIC RESPIRATORY DISEASE QUESTIONNAIRE (CRDQ)

1. I would like you to think of the activities that you have done during the last 2 weeks that have made you feel short of breath. These should be activities which you do frequently and which are important in your day to day life. Please list as many activities as you can that you have done during the last 2 weeks that have made you short of breath.

[Interviewer notes: Circle the number on the answer sheet list below for each activity mentioned. If an activity mentioned is not on the list, write it in, in the respondent's own words, in the space provided.]

Can you think of any other activities you have done during the last 2 weeks that have made you feel short of breath?

Other activities: _____

_____

_____

[Interviewer notes: Record additional items]

2. I will now read a list of activities which make some people with lung problems feel short of breath. I will pause after each item long enough for you to tell me if you have felt short of breath doing that activity during the last 2 weeks. If you haven't done the activity during the last 2 weeks, just answer "no". The activities are:

1. Being angry or upset	14. Playing sports
2. Having a bath or shower	15. Reaching over your head
3. Bending	16. Running, such as for a bus
4. Carrying, such as carrying groceries	17. Shopping
5. Dressing	18. While trying to sleep
6. Eating	19. Talking
7. Going for a walk	20. Vacuuming
8. Doing your housework	21. Walking around your own home
9. Hurrying	22. Walking uphill
10. Making a bed	23. Walking upstairs
11. Mopping or scrubbing the floor	24. Walking with others on level ground
12. Moving furniture	25. Preparing meals
13. Playing with children or grandchildren	

[Interviewer notes: Read items, omitting those which respondent has volunteered spontaneously. Pause after each item to give respondent a chance to indicate whether he/she has been short of breath while performing that activity during the last week. Circle the number adjacent to appropriate items on answer sheet above.]

3 (a) Of the items which you have listed, which is the most important to you in your day to day life? I will read through the items, and when I am finished, I would like you to tell me which is the most important.

[Interviewer notes: Read through all the items spontaneously volunteered and those from the list which patient mentioned.]

Which of these items is most important to you in your day to day life?

[Interviewer notes: List item on the response sheet]

3 (b) Of the remaining items, which is the most important to you in your day to day life? I will read through the items, and when I am finished I would like you to tell me which is the most important.

[Interviewer notes: Read through remaining items]

Which of these items is most important to you in your day to day life?

[Interviewer notes: List item on the response sheet]

3 (c) Of the remaining items, which is the most important to you in your day to day life?

[Interviewer notes: List item on the response sheet]

3 (d) Of the remaining items, which is the most important to you in your day to day life?

[Interviewer notes: List item on the response sheet]

3 (e) Of the remaining items, which is the most important to you in your day to day life?

[Interviewer notes: List item on the response sheet]

[Interviewer notes: For all subsequent questions, ensure respondent has appropriate response card in front of them before starting question.]

4. I would now like to ask you to describe how much shortness of breath you have experienced during the last 2 weeks while doing the five most important activities you have selected.

(a) Please indicate how much shortness of breath you have had during the last 2 weeks while ***[INTERVIEWER: INSERT ACTIVITY LISTED IN 3a]*** by choosing one of the following options from the card in front of you: **[green card]**

1. Extremely short of breath 2. Very short of breath 3. Quite a bit short of breath	4. Moderate shortness of breath 5. Some shortness of breath 6. A little shortness of breath 7. Not at all short of breath

(b) Please indicate how much shortness of breath you have had during the last 2 weeks while ***[INTERVIEWER: INSERT ACTIVITY LISTED IN 3b]*** by choosing one of the following options from the card in front of you: **[green card]**

1. Extremely short of breath	4. Moderate shortness of breath
2. Very short of breath	5. Some shortness of breath
3. Quite a bit short of breath	6. A little shortness of breath
	7. Not at all short of breath

(c) Please indicate how much shortness of breath you have had during the last 2 weeks while ***[INTERVIEWER: INSERT ACTIVITY LISTED IN 3c]*** by choosing one of the following options from the card in front of you: **[green card]**

1. Extremely short of breath	4. Moderate shortness of breath
2. Very short of breath	5. Some shortness of breath
3. Quite a bit short of breath	6. A little shortness of breath
	7. Not at all short of breath

(d) Please indicate how much shortness of breath you have had during the last 2 weeks while ***[INTERVIEWER: INSERT ACTIVITY LISTED IN 3d]*** by choosing one of the following options from the card in front of you: **[green card]**

1. Extremely short of breath	4. Moderate shortness of breath
2. Very short of breath	5. Some shortness of breath
3. Quite a bit short of breath	6. A little shortness of breath
	7. Not at all short of breath

(e) Please indicate how much shortness of breath you have had during the last 2 weeks while ***[INTERVIEWER: INSERT ACTIVITY LISTED IN 3e]*** by choosing one of the following options from the card in front of you: **[green card]**

1. Extremely short of breath	4. Moderate shortness of breath
2. Very short of breath	5. Some shortness of breath
3. Quite a bit short of breath	6. A little shortness of breath
	7. Not at all short of breath

5. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient? Please indicate how often during the last 2 weeks you have felt frustrated or impatient by choosing one of the following options from the card in front of you: **[blue card]**

1. All of the time	4. Some of the time
2. Most of the time	5. A little of the time
3. A good bit of the time	6. Hardly any of the time
	7. None of the time

6. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath? Please indicate how often you had difficulty getting your breath by choosing one of the following options from the card in front of you: **[blue card]**

1. All of the time 2. Most of the time 3. A good bit of the time	4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

7. What about fatigue? How tired have you felt over the last 2 weeks? Please indicate how tired you have felt over the last 2 weeks by choosing one of the following options from the card in front of you: **[orange card]**

1. Extremely tired 2. Very tired 3. Quite a bit tired	4. Moderately tired 5. Somewhat tired 6. A little tired 7. Not at all tired

8. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing? Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by choosing one of the following options from the card in front of you: **[blue card]**

1. All of the time 2. Most of the time 3. A good bit of the time	4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

9. In the last 2 weeks how much of the time did you feel very confident and sure that you could deal with your illness? Please indicate how much of the time you felt very confident and sure that you could deal with your illness by choosing one of the following options from the card in front of you: **[yellow card]**

1. None of the time 2. A little of the time 3. Some of the time	4. A good bit of the time 5. Most of the time 6. Almost all of the time 7. All of the time

10. How much energy have you had in the last 2 weeks? Please indicate how much energy you have had by choosing one of the following options from the card in front of you: **[pink card]**

1. No energy at all 2. A little energy 3. Some energy	4. Moderately energetic 5. Quite a bit of energy 6. Very energetic 7. Full of energy

11. In general, how much of the time did you feel upset, worried or depressed during the last 2 weeks? Please indicate how much of the time you felt upset, worried, or depressed during the last 2 weeks by choosing one of the following options from the card in front of you: **[blue card]**

1. All of the time 2. Most of the time 3. A good bit of the time	4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

12. How often during the last 2 weeks did you feel you had complete control of your breathing problems with shortness of breath and tiredness? Please indicate how often you felt you had complete control of you breathing problems by choosing one of the following options from the card in front of you: **[yellow card]**

1. None of the time 2. A little of the time 3. Some of the time	4. A good bit of the time 5. Most of the time 6. Almost all of the time 7. All of the time

13. How much of the time during the last 2 weeks did you feel relaxed and free of tension? Please indicate how much of the time you felt relaxed and free of tension by choosing one of the following options from the card in front of you: **[yellow card]**

1. None of the time 2. A little of the time 3. Some of the time	4. A good bit of the time 5. Most of the time 6. Almost all of the time 7. All of the time

14. How often during the last 2 weeks have you felt low in energy? Please indicate how often during the last 2 weeks you have felt low in energy by choosing one of the following options from the card in front of you: **[blue card]**

1. All of the time 2. Most of the time 3. A good bit of the time	4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

15. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps? Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by choosing one of the following options from the card in front of you: **[blue card]**

1. All of the time 2. Most of the time 3. A good bit of the time	4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

16. How often during the last 2 weeks have you felt worn out or sluggish? Please indicate how much of the time you felt worn out or sluggish by choosing one of the following options from the card in front of you: **[blue card]**

1. All of the time 2. Most of the time 3. A good bit of the time	4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

17. How happy, satisfied or pleased have you been with your personal life during the last 2 weeks? Please indicate how happy, satisfied or pleased you have been by choosing one of the following options from the card in front of you: **[grey card]**

1. Very dissatisfied, unhappy most of the time 2. Generally dissatisfied, unhappy 3. Somewhat dissatisfied, unhappy	4. Generally satisfied, pleased 5. Happy most of the time 6. Very happy most of the time 7. Extremely happy, couldn't have been more satisfied or pleased

18. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath? Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by choosing one of the options from the card in front of you: **[blue card]**

1. All of the time 2. Most of the time 3. A good bit of the time	4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

19. In general, how often during the last 2 weeks have you felt restless, tense or uptight? Please indicate how often you have felt restless, tense or uptight by choosing one of the following options from the card in front of you: **[blue card]**

1. All of the time 2. Most of the time 3. A good bit of the time	4. Some of the time 5. A little of the time 6. Hardly any of the time 7. None of the time

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